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(54) Title: 3-PYRIDYL OR 4-ISOQUINOLINYL THIAZOLES AS C17,20 LYASE INHIBITORS

(57) Abstract: The invention provides novel thiazoles bearing 3-pyridyl or 4-isoquinilnyl substituents, and pharmaceutical compositions thereof. The invention also provides methods of using compounds of the invention and pharmaceutical compositions thereof as inhibitors of lyases, e.g., the 17 α -hydroxylase-C17,20 enzyme. The invention further provides methods for treating cancer in a subject, comprising administering to the subject a compound of the invention or a pharmaceutical composition thereof. The cancer can be, e.g., prostate cancer or breast cancer.



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APPLICATION FOR PATENT

*3-Pyridyl or 4-isoquinolinyl Thiazoles
as C17,20 Lyase Inhibitors*

5

Background of the Invention

Steroid biosynthesis begins in cells of the adrenal gland where the initial product in
sterol biosynthesis, cholesterol, is converted into the adrenal steroid hormones aldosterone,
hydrocortisone, and corticosterone by a series of P₄₅₀ -mediated hydroxylation steps. The
cholesterol side-chain cleavage activity that represents the first step in steroid hormone
biosynthesis is a P₄₅₀ -mediated oxidation and cleavage of a pair of adjacent methylene
groups to two carbonyl fragments, pregnenolone and isocaprylaldehyde (see Walsh (1979)
Enzymatic Reaction Mechanisms; W.H. Freeman and Company, pp. 474-77). Another
critical set of enzymatic conversions in steroid metabolism is facilitated by 17- α -
hydroxylase-17,20-lyase (CYP17, P₄₅₀ 17). CYP17 is a bifunctional enzyme which
possesses both a C17,20-lyase activity and a C17-hydroxylase activity. Significantly, these
two alternative enzymatic activities of CYP17 result in the formation of critically different
intermediates in steroid biosynthesis and each activity appear to be differentially and
developmentally regulated (see e.g. l'Allemand et al. (2000) Eur. J. Clin. Invest. 30: 28-33).

The C17,20-lyase activity of CYP17 catalyzes the conversion of 17 α -hydroxy-
pregnenolone-and-17 α -hydroxy-progesterone-to-dehydroepiandrosterone-(DHEA)-and-
delta4-androstenedione (androstenedione) respectively. Both DHEA and androstenedione
lyase products are key intermediates in the synthesis of not only the androgens testosterone
and dihydrotestosterone (DHT), but also the estrogens 17-beta-estradiol and estrone. Indeed,
adrenal and ovarian estrogens are the main sources of estrogens in postmenopausal women
(see e.g. Harris et al. (1988) Br. J. Cancer 58: 493-6). In contrast, the C17-hydroxylase
activity of CYP17 catalyzes the conversion of the common intermediate progesterone to 17-
hydroxyprogesterone, a precursor of cortisol. Therefore the first activity of CYP17, the
C17-hydroxylase activity, promotes the formation of glucocorticoids while the second
activity of CYP17, the C17,20-lyase activity, promotes the formation of sex hormones -
particularly androgens including testosterone as well as estrogens.

Prostate cancer is currently one of the most frequently diagnosed forms of cancer in men in the U.S. and Europe. Prostate cancer is typically androgen-dependent and, accordingly, the reduction in androgen production via surgical or pharmacological castration remains the major treatment option for this indication. However, complete rather than partial withdrawal of androgens may be more effective in treating prostate cancer (Labrie, F. *et al.*, *Prostate*, 1983, 4, 579 and Crawford, E.D. *et al.*, *N. Engl. J. Med.*, 1989, 321, 419). Pharmacological inhibition of CYP17 may be a promising alternative treatment to antiandrogens and LHRH agonists in that testicular, adrenal, and peripheral androgen biosynthesis would be reduced rather than only testicular androgen production (Njar V, *et al.*, *J. Med. Chem.*, 1998, 41, 902). One such CYP17 inhibitor, the fungicide ketoconazole, has been used previously for prostate cancer treatment (Trachtenberg, J., *J. Urol.*, 1984, 132, 61 and Williams, G. *et al.*, *Br. J. Urol.*, 1986, 58, 45). However, this drug is a relatively non-selective inhibitor of cytochrome P450 (CYP) enzymes, has weak CYP17 activity, and has a number of notable side effects associated with it including liver damage (De Coster, R. *et al.*, *J. Steroid Biochem. Mol. Biol.*, 1996, 56, 133 and Lake-Bakaar, G. *et al.*, *Br. Med. J.*, 1987, 294, 419).

The importance of potent and selective inhibitors of CYP17 as potential prostate cancer treatments has been the subject of numerous studies and reviews (Njar, V. *et al.*, *Curr. Pharm. Design*, 1999, 5, 163; Barrie, S.E. *et al.*, *Endocr. Relat. Cancer*, 1996, 3, 25 and Jarman, M. *et al.*, *Nat. Prod. Rep.*, 1998, 495). Finasteride, a 5 α -reductase inhibitor, is an approved treatment for benign prostatic hyperplasia (BPH), although it is only effective with patients exhibiting minimal disease. While finasteride reduces serum DHT levels, it increases testosterone levels, and may therefore be insufficient for prostate cancer treatment (Peters, D. H. *et al.*, *Drugs*, 1993, 46, 177). Certain anti-androgenic steroids, for example, cyproterone acetate (17 α -acetoxy-6-chloro-1 α , 2 α -methylene-4,6-pregnadiene-3,20-dione), have been tested as adjuvant treatments for prostate cancer. Many other steroids have been tested as hydroxylase/lyase inhibitors. See, for example, PCT Specification WO 92/00992 (Schering AG) which describes anti-androgenic steroids having a pyrazole or triazole ring fused to the A ring at the 2,3-position, or European specifications EP-A288053 and EP-A413270 (Merrell Dow) which propose 17 β -cyclopropylamino-androst-5-en-3 β -ol or -4-en-3-one and their derivatives.

In addition to the use of CYP17 inhibitors in the treatment of prostate cancer, a second potential indication would be for estrogen-dependent breast cancer. In postmenopausal patients with advanced breast cancer, treatment with high doses of ketoconazole resulted in suppression of both testosterone and estradiol levels, implicating CYP17 as a potential target for hormone therapy (Harris, A. L. *et al.*, *Br. J. Cancer*, 1988, 58, 493).

Chemotherapy is usually not highly effective, and is not a practical option for most patients with prostate cancer because of the adverse side effects which are particularly detrimental in older patients. However, the majority of patients initially respond to hormone ablative therapy although they eventually relapse, as is typical with all cancer treatments (McGuire, in: *Hormones and Cancer*, Jacobelli *et al.* Eds.; Raven Press, New York, 1980, Vol. 15, 337-344). Current treatment by orchidectomy or administration of gonadotropin-releasing hormone (GnRH) agonists results in reduced androgen production by the testis, but does not interfere with androgen synthesis by the adrenals. Following three months of treatment with a GnRH agonist, testosterone and DHT concentrations in the prostate remained at 25% and 10%, respectively, of pretreatment levels (Forti *et al.*, *J. Clin. Endocrinol. Metab.*, 1989, 68, 461). Similarly, about 20% of castrated patients in relapse had significant levels of DHT in their prostatic tissue (Geller *et al.*, *J. Urol.*, 1984, 132, 693). These findings suggest that the adrenals contribute precursor androgens to the prostate. This is supported by clinical studies of patients receiving combined treatment with either GnRH or orchidectomy and an anti-androgen, such as flutamide, to block the actions of androgens, including adrenal androgens. Such patients have increased progression-free survival time compared to patients treated with GnRH agonist or orchidectomy alone (Crawford *et al.*, *N. Engl. J. Med.*, 1989, 321, 419 and Labrie *et al.*, *Cancer Suppl.*, 1993, 71, 1059).

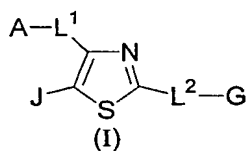
Although patients initially respond to endocrine therapy, they frequently relapse. It was reported recently that in 30% of recurring tumors of patients treated with endocrine therapy, high-level androgen receptor (AR) amplification was found (Visakorpi, *et al.*, *Nature Genetics*, 1995, 9, 401). Also, flutamide tends to interact with mutant ARs, and stimulate prostatic cell growth. This suggests that AR amplification may facilitate tumor cell growth in low androgen concentrations. Thus, total androgen blockade as first line therapy may be more effective than conventional androgen deprivation by achieving maximum suppression of androgen concentrations which may also prevent AR

amplification. It is presently unclear whether sequential treatment with different agents can prolong the benefits of the initial therapy. This strategy has been found effective in breast cancer treatment. New agents which act by different mechanisms could produce second responses in a portion of relapsed patients. Although the percentage of patients who respond to second-line hormonal therapy may be relatively low, a substantial number of patients may benefit because of the high incidence of prostate cancer. Furthermore, there is the potential for developing more potent agents than current therapies, none of which are completely effective in blocking androgen effects.

The need exists for C17,20 lyase inhibitors that overcome the above-mentioned deficiencies.

Summary of the Invention

The invention provides substituted 3-pyridyl heterocyclic compounds which inhibit the lyase activity of enzymes, e.g., 17 α -hydroxylase-C17,20 lyase. The compounds of the invention have the formula (I)



In formula (I),

L¹ represents

a chemical bond;

a carbonyl group;

-(CH₂)_a- in which a is 1, 2, or 3;

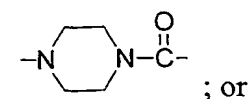
-CH₂O-;

-OCH₂-;

-O-;

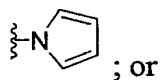
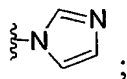
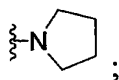
-N(R¹)- in which R¹ represents H or C₁₋₄ alkyl;

-NHC(O)-;

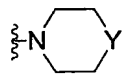


-CH₂NHC(O)-.

R^5 represents

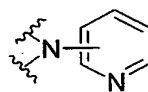


; or

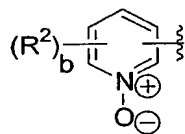


; in which

Y represents $N(R^1)$, O, S, or

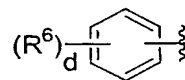


When L^1 is a bond, A may also be



• , provided that G is other than a pyridyl or an N-oxide-containing group.

When L^1 is a bond, A may also be



• ; in which

d is 0, 1, or 2 ; and

R^6 is selected from

$\overline{C_{1-6} \text{ alkyl}}$;

C_{1-4} haloalkyl ;

OR^7 ; in which

R^7 represents H, C_{1-4} alkyl, C_{1-4} haloalkyl, phenyl, benzyl, or pyridyl optionally substituted by C_{1-3} haloalkyl;

halogen;

NO_2 ;

CN;

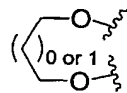
CO_2R^1 ;

C_{1-4} acyl ;

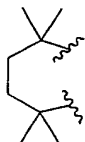
phenyl optionally substituted by halogen ;

benzyl ;

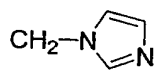
$N(R_1)^2$;



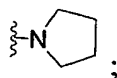
in which the O atoms are bonded to the phenyl ring at adjacent carbons;



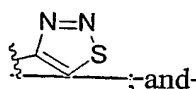
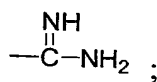
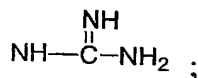
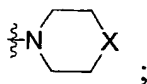
in which the terminal carbons are bonded to the phenyl ring at adjacent carbons;



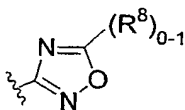
optionally substituted by halogen;



$OC(O)C_6H_5$;

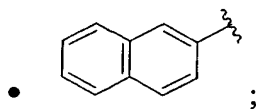


and



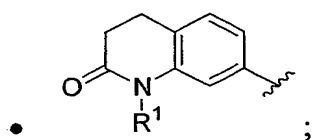
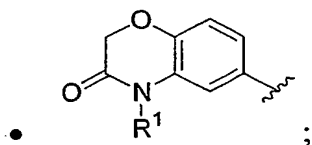
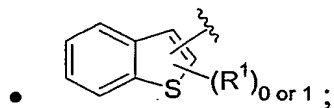
wherein R^8 represents C_{1-4} alkyl or phenyl optionally substituted by halogen.

When L^1 is a bond, A may also be

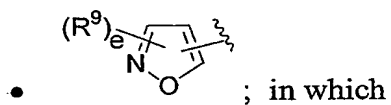


• C_{3-8} cycloalkyl ;

- C₅₋₆ cycloalkenyl ;
- adamantyl ;
- norbornyl;

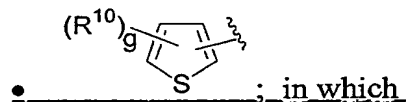
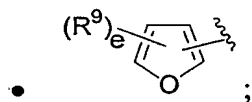


- N(R¹)₂ ;



e is 0, 1, or 2; and

R⁹ represents C₁₋₄ alkyl or phenyl optionally substituted by halogen;

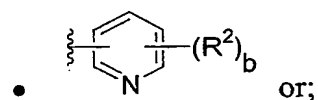


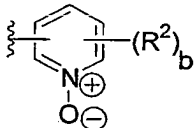
g is 0, 1, or 2; and

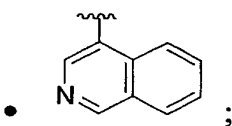
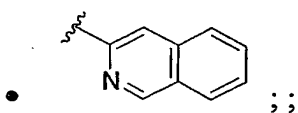
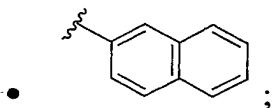
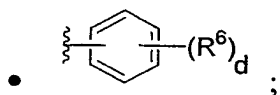
R¹⁰ represents CN, NO₂, or halogen.

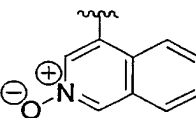
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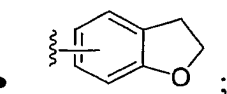
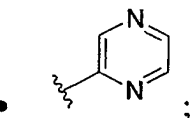
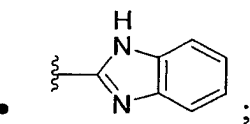
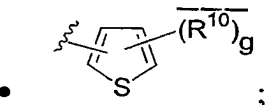
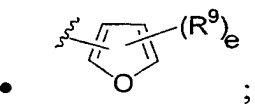
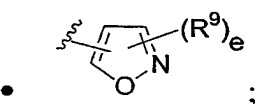
2) when L² is a bond, G represents

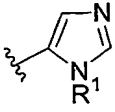
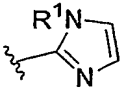
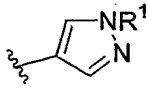
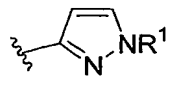
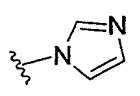
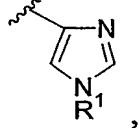
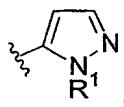
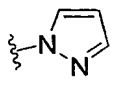


-  , provided that A is other than a pyridyl or an N-oxide-containing group;



-  , provided that A is other than a pyridyl or an N-oxide-containing group;

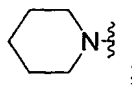
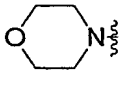



- a diazole selected from , , , ,
- ,
- ,
- , and ; or
- a triazole.

5

Furthermore,

3) when L^1 is carbonyl, A represents

- ;
- ; or
- $R^{11}N$ ; in which

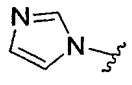
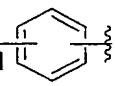
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R^{11} represents H, C_{1-4} alkyl, or phenyl optionally substituted by halogen;

Furthermore,

4) when L^1 is $-(CH_2)_a-$, A represents

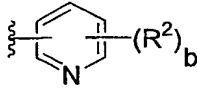
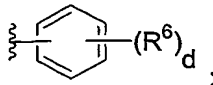
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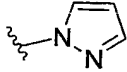
- ; or
- $(R^6)_d$ .

Furthermore,

5) when L^2 is $-(CH_2)_a-$, G represents

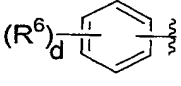
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- ;
- .

-  ; or
- a triazole.

Furthermore,

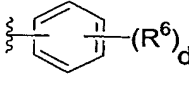
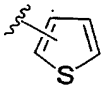
5 6) when L^1 is $-\text{CH}_2\text{O}-$, $-\text{OCH}_2-$ or O , A represents

-  ;
- C_{1-4} alkyl;
- C_{3-8} cycloalkyl; or
- C_{6-7} bicycloalkyl.

10

Furthermore,

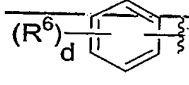
7) when L^2 is $-\text{CH}_2\text{O}-$, G represents

-  ; or
- .

15

Furthermore,

8) when L^1 is $-\text{N}(\text{R}^1)-$, A represents

-  ; or
- C_{5-6} cycloalkyl.

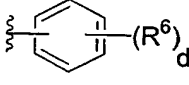
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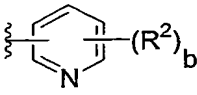
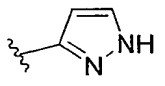
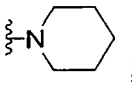
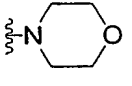
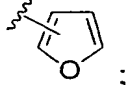
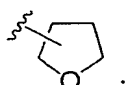
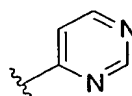
Furthermore,

9) when L^2 is $-\text{N}(\text{R}^1)-$ or $-\text{NH}(\text{CH}_2)_a-$, G represents

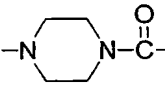
- C_{1-6} alkyl;
- C_{3-6} cycloalkyl;
- $\text{N}(\text{R}^1)_2$;

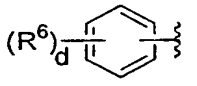
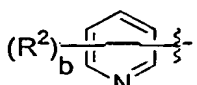
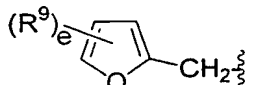

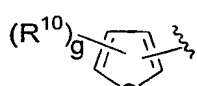
25

- .

-  ;
-  ;
-  ;
-  ;
-  ;
-  ; or
-  .

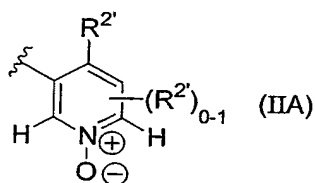
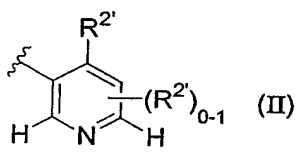
Furthermore,

10) when L^1 is $-\text{NHC(O)}-$, , or $-\text{CH}_2\text{NHC(O)}-$, A represents

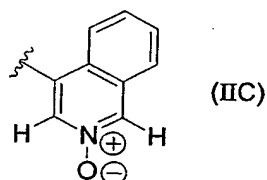
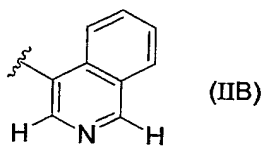
-  ;
-  ;
- C_{5-6} cycloalkyl;
- C_{7-8} bicycloalkyl;
-  ;
-  ; or
-  .

Furthermore,

- 11) one of A and G is a 3-pyridyl moiety of formula (II) or (IIA), or a 4-isoquinolyl moiety of formula (IIB) or (IIC)



, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;



, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;

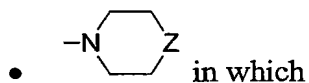
~~and this 3-pyridyl or 4-isoquinolyl moiety is joined to the thiazole ring via a chemical bond L¹ or L² respectively; and the other of A and G is as defined above.~~

In addition, when the other of A and G is joined to the thiazole ring via linker L¹ or L² respectively where L¹ or L² is not a chemical bond, then R^{2'} of formulae (II) and (IIA) is R²; but when each of A and G is joined to the thiazole ring via a chemical bond L¹ and L² respectively, then R^{2'} of formulae (II) and (IIA) is selected from the group consisting of

- C₂₋₆ alkyl, provided that when said 3-pyridyl moiety of formula (II) constitutes A, then G is other than phenyl substituted with an amide or

sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F;

- C₂₋₄ haloalkyl;
- C₄₋₆ alkoxy;
- C₃₋₆ cycloalkyl;
- phenyl optionally substituted by halogen;



Z represents CH₂, S, or N(R¹)

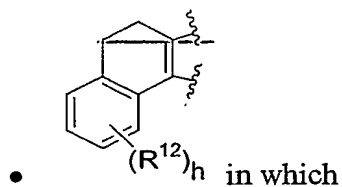
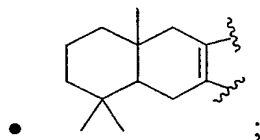
- -N(R^{3'})₂ in which

R^{3'} represents H, C₃₋₄ alkyl, C₄₋₆ cycloalkyl, or phenyl optionally substituted with halogen;

- -(CH₂)_aN(R¹)(R⁴);
- -(CH₂)_aR⁵;

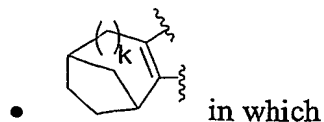
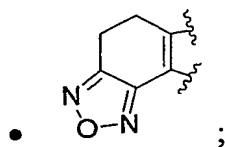
Alternatively,

12) A-L¹ and J may be joined and together with the carbon atoms to which they are connected form a ring moiety selected from the group consisting of

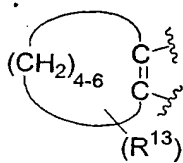


h is 0, 1, or 2; and

R¹² represents C₁₋₄ alkyl or C₁₋₄ alkoxy;



k is 0 or 1; or

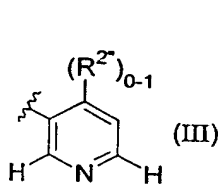


in which

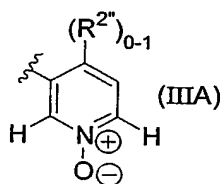
m is 0, 1, or 2;

R¹³ represents C₁₋₄ alkyl or phenyl;

said ring moiety being joined to the thiazole at the positions indicated by the truncated valences shown in the partial structures above to form a fused ring thiazole; and for these fused ring thiazoles, L² is a bond and G is a 3-pyridyl moiety of formula (III) or (IIIA)



or



in which R^{2''} is C₁₋₄ alkyl.

Pharmaceutically acceptable salts of these compounds are also within the scope of the invention.

The invention also provides pharmaceutical compositions for inhibiting lyase activity, comprising a compound of the invention plus a pharmaceutically acceptable carrier.

The invention also provides methods for inhibiting lyases, comprising contacting the lyase with a compound of the invention. In particular, the invention provides a method of inhibiting a 17 α -hydroxylase-C17,20 lyase, comprising contacting a 17 α -hydroxylase-C17,20 lyase with a compound of the invention.

The invention further provides methods for treating diseases which can benefit from an inhibition of a lyase enzyme. Exemplary diseases are lyase-associated diseases, e.g., diseases resulting from an excess of androgens or estrogens. For example, the invention provides a method for treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the invention, such that the cancer is treated.

The method of treatment may be applied where the subject is equine, canine, feline, or a primate, in particular, a human.

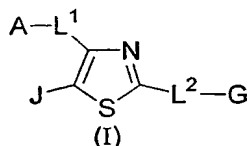
The cancer may, for example, be prostate or breast cancer. Accordingly, a method for treating prostate cancer in a subject, comprises administering to the subject a therapeutically effective amount of a compound of the invention, such that the prostate cancer in the subject is treated. Similarly, a method for treating breast cancer in a subject comprises administering to the subject a therapeutically effective amount of a compound of the invention, such that the breast cancer in the subject is treated.

10 *Detailed Description of the Invention*

The invention is based at least in part on the discovery that substituted 3-pyridyl heterocyclic compounds inhibit the enzyme 17 α -hydroxylase-C17,20 lyase.

In the broadest embodiment, the compounds of the invention have the formula (I) in which the several substituent moieties are as described in claim 1 and in the above summary of the invention.

In a preferred embodiment the compounds of the invention have the formula (I)



In formula (I),

L¹ preferably represents

- 20 a chemical bond;
- a carbonyl group;
- (CH₂)_a- in which a is 1, 2, or 3; or
- OCH₂- ;

25 L² preferably represents

- a chemical bond;
- (CH₂)_a- ; or
- N(R¹)- in which R¹ represents H or C₁₋₄ alkyl;

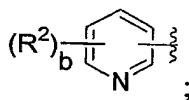
30 J preferably represents

H; or

C₁₋₄ alkyl.

Furthermore, in this preferred embodiment

1) when L¹ is a chemical bond, A represents



in which

b is 0, 1, or 2; and

R² is selected from

C₁₋₆ alkyl;

C₁₋₄ haloalkyl;

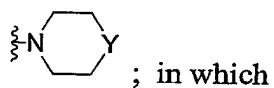
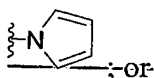
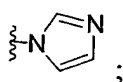
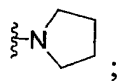
C₃₋₆ cycloalkyl;

halogen;

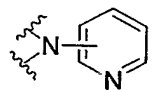
phenyl optionally substituted by halogen; and

-(CH₂)_aR⁵; in which

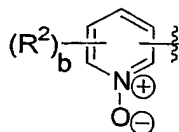
R⁵ represents



Y represents N(R¹), O, S, or

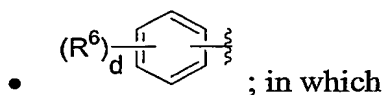


When L¹ is a bond, A may also be



, provided that G is other than a pyridyl or an N-oxide-containing group.

When L^1 is a bond, A may also be



d is 0, 1, or 2 ; and

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; in which

R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

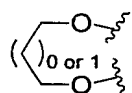
halogen;

NO_2 ;

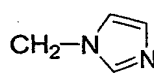
CN;

CO_2R^1 ;

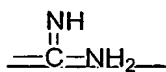
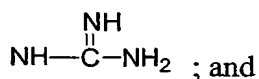
C_{1-4} acyl ;



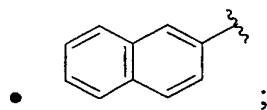
in which the O atoms are bonded to the phenyl ring at adjacent carbons;



optionally substituted by halogen;



When L^1 is a bond, A may also be

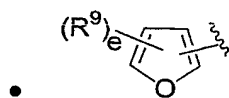


• C_{3-8} cycloalkyl ;

• C_{5-6} cycloalkenyl ;

• adamantyl ;

• norbornyl;

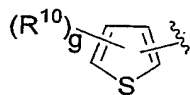


; in which

e is 0, 1, or 2; and

R⁹ represents C₁₋₄ alkyl or phenyl optionally substituted by halogen;

or

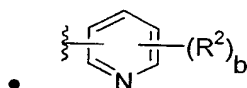


; in which

g is 0, 1, or 2; and

R¹⁰ represents CN, NO₂, or halogen.

Furthermore,

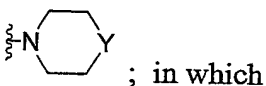
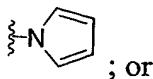
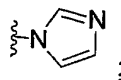
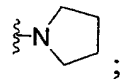
2) when L² is a bond, G preferably represents

wherein

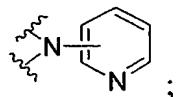
R² is selected fromC₁₋₆ alkyl;C₁₋₄ haloalkyl;C₃₋₆ cycloalkyl;

halogen;

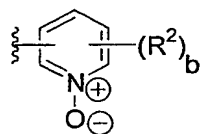
phenyl optionally substituted by halogen; and

-(CH₂)_aR⁵; in whichR⁵ represents

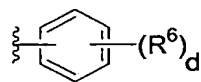
Y represents $N(R^1)$, O, S, or



or



, provided that A is other than a pyridyl or an N-oxide-containing group;



wherein

R^6 is selected from

C_{1-6} alkyl;

C_{1-4} haloalkyl;

OR^7 ; in which

R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

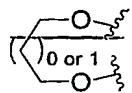
halogen;

NO_2 ;

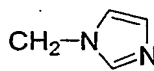
CN;

CO_2R^1 ;

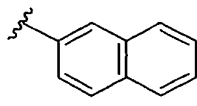
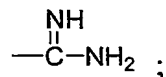
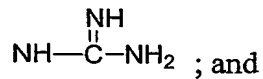
C_{1-4} acyl;

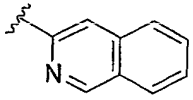
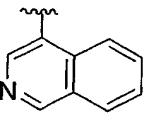
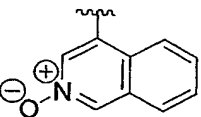
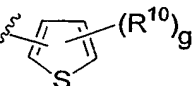
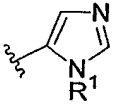
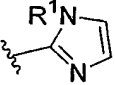
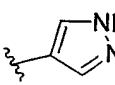
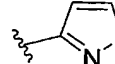
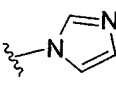
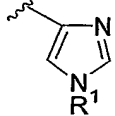
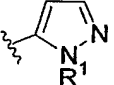
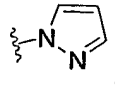


in which the O atoms are bonded to the phenyl ring at adjacent carbons;



optionally substituted by halogen;

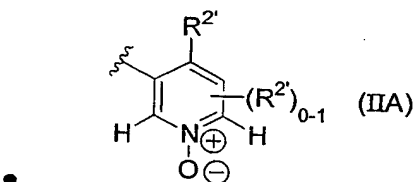
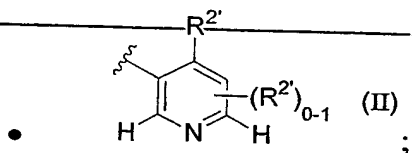


-  ; ;
-  ;
-  , provided that A is other than a pyridyl or an N-oxide-containing group;
- 5 •  ;
- a diazole selected from  ,  ,  ,  ,  ,  ,  , and  ; or
- a triazole.

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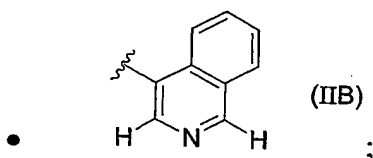
Furthermore,

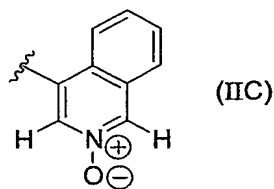
- 11) one of A and G is a 3-pyridyl moiety of formula (II) or (IIA), or a 4-isoquinolyl moiety of formula (IIB) or (IIC)



, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;

15



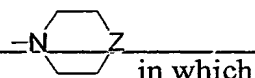


, provided that the other of A and G is other than a
pyridyl or an N-oxide-containing group;

and this 3-pyridyl or 4-isoquinolyl moiety is joined to the thiazole ring via a
chemical bond L^1 or L^2 respectively; and the other of A and G is as defined
above.

In addition, when the other of A and G is joined to the thiazole ring via linker
 L^1 or L^2 respectively where L^1 or L^2 is not a chemical bond, then $R^{2'}$ of formulae
(II) and (IIA) is R^2 ; but when each of A and G is joined to the thiazole ring via a
chemical bond L^1 and L^2 respectively, then $R^{2'}$ of formulae (II) and (IIA) is
selected from the group consisting of

- C_{2-6} alkyl, provided that when said 3-pyridyl moiety of formula (II)
constitutes A, then G is other than phenyl substituted with an amide or
sulfonamide group; and when said 3-pyridyl moiety of formula (II)
constitutes G, then A is other than phenyl substituted with F;
- C_{3-6} cycloalkyl;
- phenyl optionally substituted by halogen;

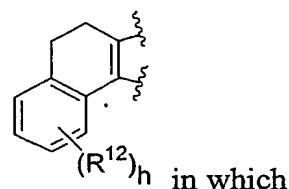


Z represents CH_2 , S, or $N(R^1)$; and

- $-(CH_2)_aR^5$.

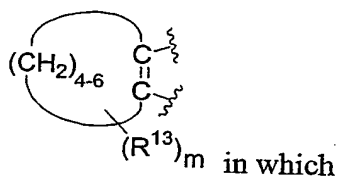
Alternatively,

12) A- L^1 and J may be joined and together with the carbon atoms to which they are
connected form a ring moiety selected from the group consisting of



h is 0, 1, or 2; and

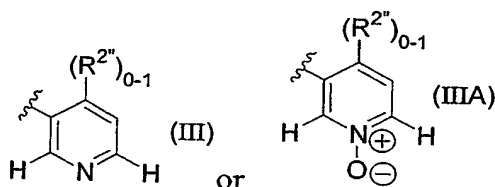
R^{12} represents C_{1-4} alkyl or C_{1-4} alkoxy; and



m is 0, 1, or 2;

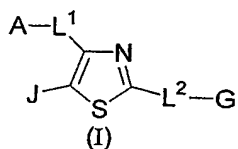
R^{13} represents C_{1-4} alkyl or phenyl;

said ring moiety being joined to the thiazole at the positions indicated by the truncated valences shown in the partial structures above to form a fused ring thiazole; and for these fused ring thiazoles, L^2 is a bond and G is a 3-pyridyl moiety of formula (III) or (IIIA)



in which $R^{2''}$ is C_{1-4} alkyl.

In a more preferred embodiment the compounds of the invention have the formula (I)



In formula (I),

L^1 more preferably represents

a chemical bond;

$-(CH_2)_a-$ in which a is 1, 2, or 3; or

$-OCH_2-$;

L^2 more preferably represents

a chemical bond;

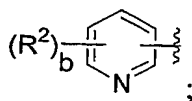
$-(CH_2)_a-$; or

$-N(R^1)-$ in which R^1 represents H or C_{1-4} alkyl; and

J more preferably represents H.

Furthermore, in this more preferred embodiment

1) when L^1 is a chemical bond, A represents



in which

b is 0, 1, or 2; and

R^2 is selected from

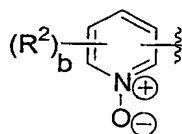
C_{1-6} alkyl;

C_{1-4} haloalkyl;

C_{3-6} cycloalkyl; and

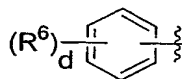
phenyl optionally substituted by halogen.

When L^1 is a bond, A may also be



containing group.

When L^1 is a bond, A may also be



d is 0, 1, or 2 ; and

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; in which

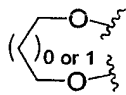
R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

halogen;

NO_2 ;

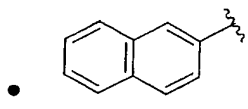
CN ;

CO_2R^1 ; and

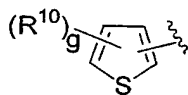


in which the O atoms are bonded to the phenyl ring at adjacent carbons.

When L^1 is a bond, A may also be



- C_{3-8} cycloalkyl ;
- C_{5-6} cycloalkenyl ;
- adamantyl ; or



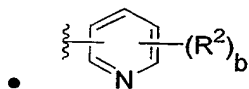
; in which

g is 0, 1, or 2; and

R^{10} represents CN, NO_2 , or halogen.

Furthermore,

2) when L^2 is a bond, G more preferably represents



wherein

R^2 is selected from

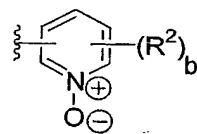
C_{1-6} alkyl;

C_{1-4} haloalkyl;

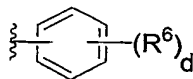
C_{3-6} cycloalkyl; and

phenyl optionally substituted by halogen;

or



, provided that A is other than a pyridyl or an N-oxide-containing group;



in which

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; in which

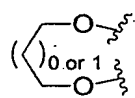
R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

halogen;

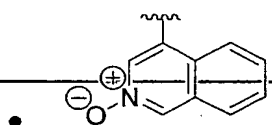
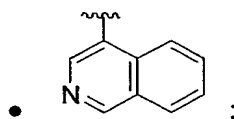
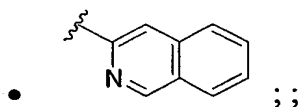
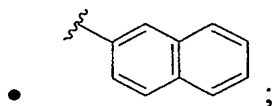
NO_2 ;

CN;

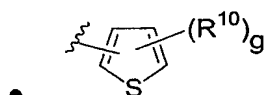
CO_2R^1 ; and



in which the O atoms are bonded to the phenyl ring at adjacent carbons;

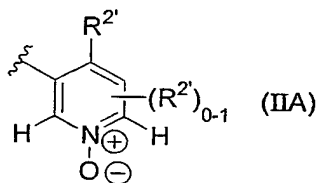
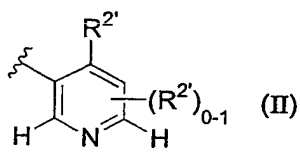


, provided that A is other than a pyridyl or an N-oxide-containing group; or

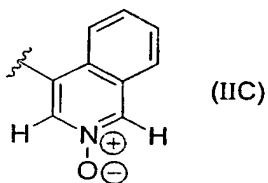
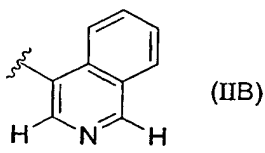


Furthermore,

11) one of A and G is a 3-pyridyl moiety of formula (II) or (IIA), or a 4-isoquinolyl moiety of formula (IIB) or (IIC)



, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;



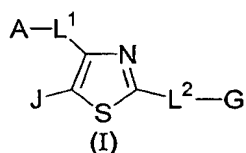
, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;

and this 3-pyridyl or 4-isoquinolyl moiety is joined to the thiazole ring via a chemical bond L¹ or L² respectively; and the other of A and G is as defined above.

~~In addition, when the other of A and G is joined to the thiazole ring via linker~~
L¹ or L² respectively where L¹ or L² is not a chemical bond, then R^{2'} of formulae (II) and (IIA) is R²; but when each of A and G is joined to the thiazole ring via a chemical bond L¹ and L² respectively, then R^{2'} of formulae (II) and (IIA) is selected from the group consisting of

- C₂₋₆ alkyl, provided that when said 3-pyridyl moiety of formula (II) constitutes A, then G is other than phenyl substituted with an amide or sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F;
- C₃₋₆ cycloalkyl; and
- phenyl optionally substituted by halogen.

In a most preferred embodiment the compounds of the invention have the formula (I)



In formula (I),

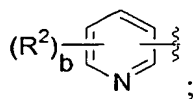
L^1 most preferably represents a chemical bond;

L^2 most preferably represents a chemical bond; and

J most preferably represents H.

Furthermore, in this most preferred embodiment

1) when L^1 is a chemical bond, A represents



in which

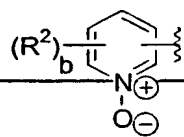
b is 0, 1, or 2; and

R^2 is selected from

C_{1-6} alkyl; and

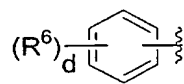
phenyl optionally substituted by halogen.

When L^1 is a bond, A may also be



, provided that G is other than a pyridyl or an N-oxide-containing group.

When L^1 is a bond, A may also be



; in which

d is 0, 1, or 2; and

R^6 is selected from

C_{1-6} alkyl;

C_{1-4} haloalkyl;

OR⁷; in which

R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

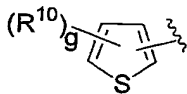
halogen;

NO_2 ; and

CN;

5

or



; in which

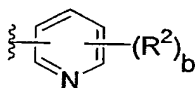
g is 0, 1, or 2; and

R^{10} represents CN, NO_2 , or halogen.

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Furthermore,

2) G most preferably represents



wherein

R^2 is selected from

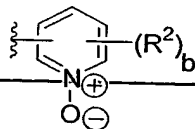
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C_{1-6} alkyl;

C_{3-6} cycloalkyl; and

phenyl optionally substituted by halogen;

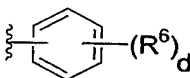
or



, provided that A is other than a pyridyl or an N-oxide-

20

containing group;



in which

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; in which

R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

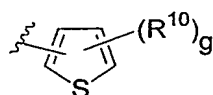
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halogen;

NO₂ ;

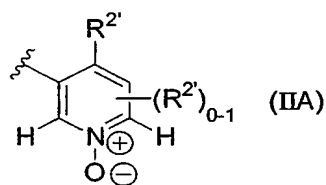
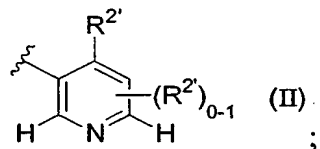
CN;

or

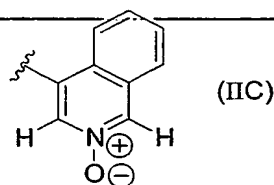
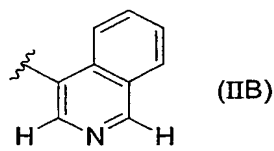


Furthermore,

11) one of A and G is a 3-pyridyl moiety of formula (II) or (IIA), or a 4-isoquinolyl moiety of formula (IIB) or (IIC)



, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;



, provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;

and this 3-pyridyl or 4- isoquinolyl moiety is joined to the thiazole ring via a chemical bond L¹ or L² respectively; and the other of A and G is as defined above.

In addition, when the other of A and G is joined to the thiazole ring via linker L^1 or L^2 respectively where L^1 or L^2 is not a chemical bond, then $R^{2'}$ of formulae (II) and (IIA) is R^2 ; but when each of A and G is joined to the thiazole ring via a chemical bond L^1 and L^2 respectively, then $R^{2'}$ of formulae (II) and (IIA) is selected from the group consisting of

- C_{2-6} alkyl, provided that when said 3-pyridyl moiety of formula (II) constitutes A, then G is other than phenyl substituted with an amide or sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F; and
- C_{3-6} cycloalkyl.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The term "agonist" of an enzyme refers to a compound that binds to the enzyme and stimulates the action of the naturally occurring enzyme, or a compound which mimics the activity of the naturally occurring enzyme.

The term "antagonist" of an enzyme refers to a compound that binds to the enzyme and inhibits the action of the naturally occurring enzyme.

The term "analog" of a compound refers to a compound having a some structural similarity to a particular compound and having essentially the same type of biological activity as the compound.

The term "CYP17 substrate" includes any of the various steroid hormones acted upon by a CYP17 or a CYP17-like P_{450} enzyme. Examples include pregnenolone, progesterone and their 17α -hydroxylated forms. Pregnenolone is converted to DHEA via a CYP17 C17,20-lyase reaction, but is also subject to C17 α -hydroxylation via the C17,20-lyase activity. Progesterone is converted to delta 4- androstenedione via a CYP17 C17,20-lyase reaction, but is also subject to C17 alpha-hydroxylation via the C17-hydroxylase activity to form 17-hydroxyl-progesterone, a precursor to hydrocortisone (i.e. cortisol).

The term "CYP17 metabolite" refers to any of the steroid hormones that are synthesized from a cholesterol precursor via a CYP17-mediated reaction, such as a C17-hydroxylase reaction or a C17,20-lyase reaction. Examples of CYP17 metabolites include the androgens, such as testosterone, which are synthesized via a CYP17 C17,20-lyase reaction from CYP17 substrate precursors such as pregnenolone (converted to DHEA by the CYP17 C17,20-lyase activity), and progesterone (converted to delta 4- androstenedione by the CYP17 C17,20-lyase activity). Progestagens such as progesterone are primarily synthesized in the corpus luteum. The androgens are responsible for, among other things, development of male secondary sex characteristics and are primarily synthesized in the testis. Other examples include the estrogens, which are also synthesized from a cholesterol precursor via a CYP17-mediated reaction. The estrogens are responsible for, among other things, the development of female secondary sex characteristics and they also participate in the ovarian cycle and are primarily synthesized in the ovary. Another group of CYP17 metabolites are the glucocorticoids, such as hydrocortisone (i.e. cortisol), which is synthesized from progesterone via a CYP17-mediated reaction. The glucocorticoids, among other functions, promote gluconeogenesis and the formation of glycogen and also enhance the degradation of fat. The glucocorticoids are primarily synthesized in the adrenal cortex.

The term "CYP17 metabolite" is further meant to include other steroid hormones which, although not necessarily synthesized by a CYP17-mediated reaction, may nonetheless be understood by the skilled artisan to be readily affected by an alteration in a CYP17-mediated activity. For example, the mineralocorticoids, such as aldosterone, are derived from cholesterol via a progesterone intermediate. Since progesterone is also converted to the glucocorticoids and sex steroids via CYP17-mediated reactions, an alteration of a CYP17 activity can alter the amount of progesterone available for conversion to aldosterone. For example, inhibition of CYP17 activity can increase the amount of progesterone available for conversion into aldosterone. Therefore, inhibition of CYP17 can lead to an increase in the level of aldosterone. The mineralocorticoids function, among other things, to increase reabsorption of sodium ions, chloride ions, and bicarbonate ions by the kidney, which leads to an increase in blood volume and blood pressure. The mineralocorticoids are primarily synthesized in the adrenal cortex.

The term "CYP17 metabolite-associated disease or disorder" refers to a disease or disorder which may be treated by alteration of the level of one or more CYP17 metabolites.

Examples include a hormone dependent cancer, such as an androgen-dependent prostate cancer, which may be treated by inhibiting CYP17-mediated androgen synthesis, and an estrogen-dependent breast cancer or ovarian cancer, which may be treated by inhibiting CYP17-mediated estrogen synthesis. Other examples of "CYP17 metabolite-associated diseases or disorders" are Cushing's disease, hypertension, prostatic hyperplasia, and glucocorticoid deficiency. Patients with Cushing's syndrome are relatively insensitive to glucocorticoid feedback and exhibit an oversecretion of cortisol devoid of a circadian cycle (see e.g. Newell-Price & Grossman (2001) *Ann. Endocrinol.* 62: 173-9). Another CYP17 metabolite-associated disease or disorder is hypertension. Mineralocorticoid excess causes hypertension by facilitating the sodium retention at renal tubules.

The term "derivative" of a compound refers to another compound which can be derived, e.g., by chemical synthesis, from the original compound. Thus a derivative of a compound has certain structural similarities with the original compound.

"Disease associated with an abnormal activity or level of a lyase" refers to diseases in which an abnormal activity or protein level of a lyase is present in certain cells, and in which the abnormal activity or protein level of the lyase is at least partly responsible for the disease.

A "disease associated with a lyase" refers to a disease that can be treated with a lyase inhibitor, such as the compounds disclosed herein.

A "lyase" refers to an enzyme having a lyase activity.

"Lyase activity" refers to the activity of an enzyme to catalyze the cleavage of the bond C17-C20 in 17 α -hydroxy-pregnenolone and 17 α -hydroxy-progesterone to form dehydroepiandrosterone (DHEA) and delta4-androstenedione, respectively. Lyase activity also refers to the cleavage of a similar bond in related compounds.

A "lyase inhibitor" is a compound which inhibits at least part of the activity of a lyase in a cell. The inhibition can be at least about 20%, preferably at least about 40%, even more preferably at least about 50%, 70%, 80%, 90%, 95%, and most preferably at least about 98% of the activity of the lyase.

A "patient" or "subject" to be treated by the subject method can mean either a human or non-human animal.

"Treating" a disease refers to preventing, curing or improving at least one symptom of a disease.

The following definitions pertain to the chemical structure of compounds:

The term "heteroatom" as used herein means an atom of nitrogen, oxygen, or sulfur.

5 The term "alkyl" refers to the radicals of saturated aliphatic groups, including straight-chain alkyl groups and branched-chain alkyl groups.

The term "cycloalkyl" (alicyclic) refers to radicals of cycloalkyl compounds, examples being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

10 The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups that contain at least one double or triple bond respectively.

15 Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group but having from one to six carbons, preferably from one to four carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls.

20 The term "aryl" as used herein means an aromatic group of 6 to 14 carbon atoms in the ring(s), for example, phenyl and naphthyl. As indicated, the term "aryl" includes polycyclic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic.

25 The term "heteroaryl" as used herein means an aromatic group which contains at least one heteroatom in at least one ring. Typical examples include 5-, 6- and 7-membered single-ring aromatic groups that may include from one to four heteroatoms. Examples include pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. These aryl groups may also be referred to as "aryl heterocycles" or "heteroaromatics."

30 The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

The terms "alkoxyl" or "alkoxy" as used herein refer to moiety in which an alkyl group is bonded to an oxygen atom, which is in turn bonded to the rest of the molecule. Examples are methoxy, ethoxy, propyloxy, *tert*-butoxy, etc.

As used herein, the term "nitro" means -NO₂; the term "halogen" designates -F, -Cl, -
5 Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means -SO₂-.

The terms triflyl, tosyl, mesyl, and nonafllyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized
10 and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl,
15 respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; (i.e., *J. Org. Chem.* **2002**, 67(1), 24A. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

20 As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom
25 and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include
30 acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for

example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the
5 heteroatoms.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of
10 protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999).

Abbreviations and Acronyms

15 When the following abbreviations are used throughout the disclosure, they have the following meaning:

A	angstroms
AcOH	acetic acid
amu	atomic mass units
20 Anal. Calcd	analysis calculated
Ar	argon
BSA	bovine serum albumin
<hr/>	
<i>n</i> -BuLi	butyllithium
CDCl ₃	chloroform- <i>d</i>
25 CD ₃ OD	methanol- <i>d</i> ₄
CHCl ₃	chloroform
CH ₂ Cl ₂	methylene chloride
CH ₃ CN	acetonitrile
CI	chemical ionization (in mass spectrometry)
30 CuI	copper iodide
Cs ₂ CO ₃	cesium carbonate
CPM	counts per minute

	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	DMSO- <i>d</i> ₆	dimethylsulfoxide- <i>d</i> ₆
	EDCI	
5	EI	electron impact (in mass spectrometry)
	EPA	Environmental Protection Agency (as in EPA vial)
	ES	electrospray ionization (in mass spectrometry)
	Et ₃ N	triethylamine
	EtOAc	ethyl acetate
10	Et ₂ O	diethyl ether
	EtOH	ethanol
	ETPB	ethyltriphenylphosphonium bromide
	g	gram
	GCEI	gas chromatography – electron impact mass spectrometry
15	GCMS	gas chromatography / mass spectrometry
	h	hour(s)
	H ₂	hydrogen gas
	HBr	hydrogen bromide
	HCl	hydrochloric acid
20	¹ H NMR	proton nuclear magnetic resonance
	HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
	HOAc	acetic acid
<hr/>		
	HOAt	n-hydroxyazatriazole
	HPLC	high performance liquid chromatography
25	H ₂ S	hydrogen sulfide
	Hz	hertz
	KHMDS	potassium bis(trimethylsilyl)amide
	KOH	potassium hydroxide
	L	liter(s)
30	LCMS	liquid chromatography / mass spectroscopy
	LDA	lithium diisopropyl amide
	M	molar
	MCPBA	m-chloroperbenzoic acid

	MeCN	acetonitrile
	MeOH	methanol
	min	minute
	μg	microgram
5	mg	milligram
	MgSO ₄	magnesium sulfate
	mL	microliter
	μm	micrometer
	μM	micromolar
10	mm	millimeter
	mmol	millimol
	mL	milliliter
	mm	millimeter
	mol	mole
15	mp	melting point
	MS	mass spectrometry
	<i>m/z</i>	mass to charge ratio
	MTBE	methyl <i>tert</i> -butyl ether
	N	normal
20	NaHCO ₃	sodium bicarbonate
	NaHMDS	sodium bis(trimethylsilyl)amide
	NaOH	sodium hydroxide
<hr/>		
	Na ₂ SO ₄	sodium sulfate
	NCS	<i>n</i> -chlorosuccinimide
25	NH ₄ Cl	ammonium chloride
	NH ₄ OH	ammonium hydroxide
	NMR	nuclear magnetic resonance
	nM	nanomolar
	PCC	pyridinium chlorochromate
30	Pd/C	palladium on carbon
	POCl ₃	Phosphorous oxychloride
	P ₂ O ₅	phosphorous pentoxide
	psi	pounds per square inch

R _f	TLC retention factor
rt	room temperature
SPA	Scintillation Proximity Assay
THF	tetrahydrofuran
5 TFA	trifluoroacetic acid
TMS	tetramethylsilane
TLC	thin layer chromatography
t _R	HPLC retention time

10 Compounds of the Invention

The present invention is directed to compounds which inhibit 17 α -hydroxylase-C17,20-lyase.

Exemplary compounds of the invention are set forth in Table 1 below. The exemplary compounds of Table 1 are producible from known compounds (or from starting materials which, in turn, are producible from known compounds), through the general preparative methods described in the Examples. The compounds are grouped in the Tables according to the method used for their synthesis, as described in the Examples.

Table 1. Exemplary Compounds of the Invention

Example #	Compound Name
1	2-(2-(3-pyridyl)-1,3-thiazol-4-yl)phenyl benzoate
2	6-(2-(3-pyridyl)-1,3-thiazol-4-yl)benzo[b]morpholin-3-one
3	3-(2-(3-pyridyl)-1,3-thiazol-4-yl)phenyl benzoate
4	5-methyl-4-phenyl-2-(3-pyridyl)-1,3-thiazole
5	4-[(4-chlorophenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
6	2-(4-methyl(3-pyridyl))-4-phenyl-1,3-thiazole
7	4-(4-chlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
8	4-methoxy-1-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene
9	4-[(3,4-dichlorophenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
10	4-[(4-methylphenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
11	4-[(3-methylphenyl)methyl]-2-(3-pyridyl)-1,3-thiazole

Example #	Compound Name
12	4-[(3-chlorophenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
13	4-[(3-nitrophenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
14	4-[(4-bromophenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
15	4-[(4-fluorophenyl)methyl]-2-(3-pyridyl)-1,3-thiazole
16	4-(2,4-dichlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
17	4-(4-chlorophenyl)-5-methyl-2-(3-pyridyl)-1,3-thiazole
18	4-(4-chlorophenyl)-5-methyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
19	4-adamantanyl-2-(3-pyridyl)-1,3-thiazole
20	4-(tert-butyl)-2-(3-pyridyl)-1,3-thiazole
21	4-cyclobutyl-2-(3-pyridyl)-1,3-thiazole
22	4-cyclopentyl-2-(3-pyridyl)-1,3-thiazole
23	(5-methyl-2-(3-pyridyl)(1,3-thiazol-4-yl))phenylamine
24	3-methoxy-1-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene
25	4-(4-fluorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
26	2-(4-methyl(3-pyridyl))-4-(3-nitrophenyl)-1,3-thiazole
27	2-(4-methyl(3-pyridyl))-4-(2-nitrophenyl)-1,3-thiazole
28	4-(3,4-difluorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
29	4-(5-chloro(2-thienyl))-2-(4-methyl(3-pyridyl))-1,3-thiazole
30	ethyl 3-methyl-3-(2-(3-pyridyl)(1,3-thiazol-4-yl))butanoate
31	2-(4-methyl(3-pyridyl))-4-(2-naphthyl)-1,3-thiazole
32	4-[(4-chlorophenyl)methyl]-2-(4-methyl(3-pyridyl))-1,3-thiazole
33	2-(4-methyl(3-pyridyl))-4-[(4-methylphenyl)methyl]-1,3-thiazole
34	4-(4-chlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
35	2-[4-(methylethyl)(3-pyridyl)]-4-phenyl-1,3-thiazole
36	4-(4-chlorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
37	4-methoxy-1-{2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)}benzene
38	4-(4-chlorophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
39	1-[2-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-4-yl)]-4-methoxybenzene
40	4-(2,4-dichlorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
41	diethyl(2-(3-pyridyl)(1,3-thiazol-4-yl))amine
42	4-cyclohexyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
43	4-adamantanyl-2-(4-methyl(3-pyridyl))-1,3-thiazole

Example #	Compound Name
44	4-(tert-butyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
45	3-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]pyridin-4-ol
46	4-(2,4-dichlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
47	4-(4-chlorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
48	4-phenyl-2-(4-phenyl(3-pyridyl))-1,3-thiazole
49	4-(4-chlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole, bromide
50	2-(4-methyl(3-pyridyl))-4-(3-pyridyl)-1,3-thiazole
51	4-methoxy-1-[2-(4-phenyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene
52	4-(2,4-dichlorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
53	4-(4-chlorophenyl)-5-methyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
54	cyclohexylmethyl[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]amine
55	4-cyclopent-1-enyl-2-(3-pyridyl)-1,3-thiazole
56	4-cyclopent-1-enyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
57	4-cyclohexyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
58	4-adamantanyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
59	4-(tert-butyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
60	4-cycloheptyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
61	2-(3-chloro-4-fluorophenyl)-4-(3-pyridyl)-1,3-thiazole
62	4-(3-pyridyl)-2-(2-thienyl)-1,3-thiazole
63	1,3-dimethoxy-2-{2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)}benzene
64	4-(4-fluorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
65	2-[4-(methylethyl)(3-pyridyl)]-4-(4-methylphenyl)-1,3-thiazole
66	4-[(4-chlorophenyl)methyl]-2-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
67	4,5-dimethyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
68	4-ethyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
69	4-ethoxy-2-(4-methyl(3-pyridyl))-1,3-thiazole
70	2-(4-methyl(3-pyridyl))-4-(methylethoxy)-1,3-thiazole
71	(3,5-dichlorophenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]amine
72	2-[4-(methylethyl)(3-pyridyl)]-4-(4-nitrophenyl)-1,3-thiazole
73	4-(3,4-dichlorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole

Example #	Compound Name
74	4-(4-chloro-3-nitrophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
75	2-methoxy-1-{2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)}benzene
76	1,4-dimethoxy-2-{2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)}benzene
77	4-(3-bromophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
78	4-(4-bromophenyl)-5-methyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
79	4-(2,4-dimethylphenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
80	4-(3-fluorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
81	4-(3,4-difluorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
82	4-(3-chlorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
83	4-(2-chlorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
84	2-[4-(methylethyl)(3-pyridyl)]-4-(2-naphthyl)-1,3-thiazole
85	2-(4-methyl(3-pyridyl))-4-(2-pyridyl)-1,3-thiazole
86	2,4-di(3-pyridyl)-1,3-thiazole
87	6-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]-1,3,4-trihydroquinolin-2-one
88	ethyl 2-(4-methyl-3-pyridyl)-1,3-thiazole-4-carboxylate
89	4-(4-bromophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
90	2-[4-(methylethyl)(3-pyridyl)]-4-(3-nitrophenyl)-1,3-thiazole
91	2-[4-(methylethyl)(3-pyridyl)]-4-(2-nitrophenyl)-1,3-thiazole
92	2-(4-cyclopropyl(3-pyridyl))-4-(4-fluorophenyl)-1,3-thiazole
93	4-(4-fluorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
94	2-(4-methyl(3-pyridyl))-4-(4-phenylphenyl)-1,3-thiazole
95	4-(4-bromophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
96	4-[3,5-bis(trifluoromethyl)phenyl]-2-(4-methyl(3-pyridyl))-1,3-thiazole
97	4-(4a,9b-dihydrobenzo[b]benzo[1,2-d]furan-8-yl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
98	4-cycloheptyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
99	2-[4-(methylethyl)(3-pyridyl)]-4-(4-phenylphenyl)-1,3-thiazole
100	4-{2-[4-(methylethyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile
101	3-{2-[4-(methylethyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile
102	trifluoro(4-{2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)}phenoxy)methane
103	difluoro(4-{2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-

Example #	Compound Name
	yl))phenoxy)methane
104	4-(2-fluorophenyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
105	2-[4-(methylethyl)(3-pyridyl)]-4-(4-pyrrolidinylphenyl)-1,3-thiazole
106	3-{2-[4-(methylethyl)-3-pyridyl]-1,3-thiazol-4-yl}phenyl benzoate
107	4-[(4-chlorophenyl)methyl]-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
108	4-cyclopentyloxy-2-(3-pyridyl)-1,3-thiazole
109	4-(methylethoxy)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
110	(3,5-dichlorophenyl){2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)}amine
111	4-(3-chloro(2-thienyl))-2-(4-methyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
112	4-(3-bromo(2-thienyl))-2-(4-methyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
113	2-(4-methyl(3-pyridyl))-4-(4-nitrophenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
114	2-methoxy-1-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene, 2,2,2-trifluoroacetic acid
115	2,4-dimethoxy-1-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene, 2,2,2-trifluoroacetic acid
116	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
117	4-cyclohexyloxy-2-(3-pyridyl)-1,3-thiazole
118	4-cyclopent-1-enyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
119	4-cyclopentyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
120	4-cyclopentyl-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
121	4-cyclopentyloxy-2-(4-methyl(3-pyridyl))-1,3-thiazole
122	4-cyclohexyloxy-2-(4-methyl(3-pyridyl))-1,3-thiazole
123	4-adamantanyl-2-(5-methyl(3-pyridyl))-1,3-thiazole
124	2-(4-cyclopentyl(3-pyridyl))-4-(4-fluorophenyl)-1,3-thiazole
125	4-(4-chlorophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
126	4-(4-bromophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
127	2-(4-cyclopentyl(3-pyridyl))-4-(4-methylphenyl)-1,3-thiazole
128	1-[2-(4-cyclopentyl(3-pyridyl))(1,3-thiazol-4-yl)]-4-methoxybenzene
129	2-(4-cyclopentyl(3-pyridyl))-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
130	4-(3-chlorophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole

Example #	Compound Name
131	4-(3-bromophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
132	3-[2-(4-cyclopentyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
133	2-(4-cyclopentyl(3-pyridyl))-4-(3-nitrophenyl)-1,3-thiazole
134	2-(4-cyclopentyl(3-pyridyl))-4-(4-phenylphenyl)-1,3-thiazole
135	2-(4-cyclopentyl(3-pyridyl))-4-(3-fluorophenyl)-1,3-thiazole
136	4-(4-chloro-3-nitrophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
137	4-(3-chlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
138	3-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
139	4-(2-chlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
140	4-(3,4-dichlorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
141	4-(2-fluorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
142	4-(3-fluorophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
143	4-(3-bromophenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole
144	difluoro {4-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} methane
145	trifluoro {4-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} methane
146	2-[4-(methylethyl)(3-pyridyl)]-4-(2-pyridyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
147	2-(3-pyridyl)-4-(4-pyridyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
148	2-(4-methyl(3-pyridyl))-4-(4-pyridyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
149	2-[4-(methylethyl)(3-pyridyl)]-4-(4-pyridyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
150	2-(4-methyl(3-pyridyl))-4-(4-pyridyl)-1,3-thiazole
151	4-cyclohexyl-2-(4-ethyl(3-pyridyl))-1,3-thiazole
152	2-(4-ethyl(3-pyridyl))-4-phenyl-1,3-thiazole
153	2-(4-ethyl(3-pyridyl))-4-(4-fluorophenyl)-1,3-thiazole
154	4-(4-chlorophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
155	4-[2-(4-ethyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
156	2-(4-ethyl(3-pyridyl))-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
157	2-(4-ethyl(3-pyridyl))-4-(4-phenylphenyl)-1,3-thiazole
158	1-[2-(4-ethyl(3-pyridyl))(1,3-thiazol-4-yl)]-4-methoxybenzene
159	{4-[2-(4-ethyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} difluoromethane

Example #	Compound Name
160	{4-[2-(4-ethyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} trifluoromethane
161	2-(4-ethyl(3-pyridyl))-4-(3-fluorophenyl)-1,3-thiazole
162	4-(3-chlorophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
163	4-(3-bromophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
164	3-[2-(4-ethyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
165	2-(4-ethyl(3-pyridyl))-4-(3-nitrophenyl)-1,3-thiazole
166	4-cyclobutoxy-2-(3-pyridyl)-1,3-thiazole
167	4-cyclobutoxy-2-(4-methyl(3-pyridyl))-1,3-thiazole
168	4-cycloheptyloxy-2-(4-methyl(3-pyridyl))-1,3-thiazole
169	4-cycloheptyloxy-2-(3-pyridyl)-1,3-thiazole
170	4-((2S)bicyclo[2.2.1]hept-2-yloxy)-2-(3-pyridyl)-1,3-thiazole
171	4-((2S)bicyclo[2.2.1]hept-2-yloxy)-2-(4-methyl(3-pyridyl))-1,3-thiazole
172	2-(4-methyl(3-pyridyl))-4-(phenylmethoxy)-1,3-thiazole
173	4-(phenylmethoxy)-2-(3-pyridyl)-1,3-thiazole
174	4-(bicyclo[2.2.1]hept-2-ylmethoxy)-2-(3-pyridyl)-1,3-thiazole
175	2-(4-ethyl(3-pyridyl))-4-(2-fluorophenyl)-1,3-thiazole
176	4-(2-chlorophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
177	2-(4-ethyl(3-pyridyl))-4-(2-nitrophenyl)-1,3-thiazole
178	1-[2-(4-ethyl(3-pyridyl))(1,3-thiazol-4-yl)]-2-methoxybenzene
179	2-(4-ethyl(3-pyridyl))-4-(2-naphthyl)-1,3-thiazole
180	2-(4-ethyl(3-pyridyl))-5-methyl-4-phenyl-1,3-thiazole
181	4-(4-chlorophenyl)-2-(4-ethyl(3-pyridyl))-5-methyl-1,3-thiazole
182	4-(4-bromophenyl)-2-(4-ethyl(3-pyridyl))-5-methyl-1,3-thiazole
183	4-(3,4-dichlorophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
184	1-[2-(4-ethyl(3-pyridyl))-5-methyl(1,3-thiazol-4-yl)]-4-methoxybenzene
185	3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)]-4-methoxypyridine
186	2-(4-chloro(3-pyridyl))-4-(4-chlorophenyl)-1,3-thiazole, hydrogen chloride
187	4-(4-chloro-3-nitrophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
188	2-[2-(4-ethyl(3-pyridyl))(1,3-thiazol-4-yl)]-1,4-dimethoxybenzene
189	4-(2,4-dichlorophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
190	2-(4-cyclopropyl(3-pyridyl))-4-(4-phenylphenyl)-1,3-thiazole
191	{4-[2-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-4-

Example #	Compound Name
	yl)]phenoxy} difluoromethane
192	2-(4-cyclopropyl(3-pyridyl))-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
193	{4-[2-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} trifluoromethane
194	4-(4-chlorophenyl)-2-(4-cyclopropyl(3-pyridyl))-5-methyl-1,3-thiazole
195	4-(4-bromophenyl)-2-(4-cyclopropyl(3-pyridyl))-5-methyl-1,3-thiazole
196	2-(4-cyclopropyl(3-pyridyl))-5-methyl-4-phenyl-1,3-thiazole
197	1-[2-(4-cyclopropyl(3-pyridyl))-5-methyl(1,3-thiazol-4-yl)]-4-methoxybenzene
198	4-[2-(4-cyclopropyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
199	4-(2,4-dimethylphenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
200	4-cyclohexyl-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
201	4-cyclohexyl-5-methyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
202	4-cyclohexyl-5-iodo-2-(4-methyl(3-pyridyl))-1,3-thiazole
203	4-cyclohexyl-2-[4-(2-methylpropyl)(3-pyridyl)]-1,3-thiazole
204	4-(bicyclo[2.2.1]hept-2-ylmethoxy)-2-(4-methyl(3-pyridyl))-1,3-thiazole
205	4-(4-chlorophenyl)-5-iodo-2-(4-methyl(3-pyridyl))-1,3-thiazole
206	4-(3,4-difluorophenyl)-5-iodo-2-(4-methyl(3-pyridyl))-1,3-thiazole
207	4-(4-chlorophenyl)-5-ethyl-2-(4-propyl(3-pyridyl))-1,3-thiazole
208	4-(4-chlorophenyl)-2-[4-(2-methylpropyl)(3-pyridyl)]-1,3-thiazole
209	2-(4-butyl(3-pyridyl))-4-(4-chlorophenyl)-5-propyl-1,3-thiazole
210	4-adamantanyl-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
211	4-(3-bromophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
212	3-[2-(4-cyclopropyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
213	2-(4-cyclopropyl(3-pyridyl))-4-(2-nitrophenyl)-1,3-thiazole
214	4-(3,4-dichlorophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
215	2-(4-cyclopropyl(3-pyridyl))-4-(2-naphthyl)-1,3-thiazole
216	1-[2-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-4-yl)]-2-methoxybenzene
217	4-(2,4-dimethylphenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
218	2-[2-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-4-yl)]-1,4-dimethoxybenzene
219	4-(4-chloro-3-nitrophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
220	2-(4-cyclopropyl(3-pyridyl))-4-(2-fluorophenyl)-1,3-thiazole
221	2-(4-methyl(3-pyridyl))-4-(4-nitrophenyl)-1,3-thiazole

Example #	Compound Name
222	4-(5-chloro(2-thienyl))-2-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
223	4-(3-chlorophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
224	4-(2-chlorophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
225	2-(4-cyclopropyl(3-pyridyl))-4-phenyl-1,3-thiazole
226	2-(4-cyclopropyl(3-pyridyl))-4-(3-fluorophenyl)-1,3-thiazole
227	2-(4-cyclopropyl(3-pyridyl))-4-(4-methylphenyl)-1,3-thiazole
228	2-(4-cyclopropyl(3-pyridyl))-4-(3-nitrophenyl)-1,3-thiazole
229	2-(4-cyclopropyl(3-pyridyl))-4-(4-nitrophenyl)-1,3-thiazole
230	4-(4-bromophenyl)-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole
231	2-(4-cyclopropyl(3-pyridyl))-4-(3-pyridyl)-1,3-thiazole
232	2-(4-cyclopropyl(3-pyridyl))-4-(4-methyl(3-pyridyl))-1,3-thiazole
233	2-(4-cyclopropyl(3-pyridyl))-4-(2-pyridyl)-1,3-thiazole
234	2-(4-cyclopropyl(3-pyridyl))-4-(4-pyridyl)-1,3-thiazole
235	2-(4-methyl(3-pyridyl))-4-(2-pyridyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
236	4-(2,4-dimethylphenyl)-2-(4-methyl(3-pyridyl))-1,3-thiazole, bromide
237	2-(4-ethyl(3-pyridyl))-4-(3-pyridyl)-1,3-thiazole
238	2-(4-ethyl(3-pyridyl))-4-(4-methylphenyl)-1,3-thiazole
239	4-(4-bromophenyl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
240	2-(4-ethyl(3-pyridyl))-4-(4-nitrophenyl)-1,3-thiazole
241	4-(2H,3H-benzo[3,4-e]1,4-dioxan-6-yl)-2-(4-ethyl(3-pyridyl))-1,3-thiazole
242	2-(4-ethyl(3-pyridyl))-5-methyl-4-[4-(2-methylpropyl)phenyl]-1,3-thiazole
243	4-adamantanyl-2-(4-ethyl(3-pyridyl))-1,3-thiazole
244	4-(4-chlorophenyl)-2-(4-piperidyl(3-pyridyl))-1,3-thiazole
245	4-(4-chlorophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
246	2-(4-butyl(3-pyridyl))-4-(4-chlorophenyl)-1,3-thiazole
247	4-(4-chlorophenyl)-5-ethyl-2-(4-methyl(3-pyridyl))-1,3-thiazole
248	4-(4-chlorophenyl)-2-(4-methyl(3-pyridyl))-5-propyl-1,3-thiazole
249	2-[4-(methylethyl)(3-pyridyl)]-4-(3-pyridyl)-1,3-thiazole
250	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](2-morpholin-4-ylethyl)amine, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid

Example #	Compound Name
251	4-(4-chlorophenyl)-2-(4-piperazinyl(3-pyridyl))-1,3-thiazole
252	{3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)](4-pyridyl)}cyclobutylamine
253	{3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)](4-pyridyl)}propylamine
254	{3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)](4-pyridyl)}(methylpropyl)amine
255	4-(4-chlorophenyl)-2-(4-morpholin-4-yl(3-pyridyl))-1,3-thiazole
256	{3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)](4-pyridyl)}(4-fluorophenyl)amine
257	4-{3-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]-4-pyridyl}-1,4-thiazaperhydroine
258	{3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)](4-pyridyl)}phenylamine
259	2-(4-cyclopentyl(3-pyridyl))-4-phenyl-1,3-thiazole
260	4-(2-chlorophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
261	4-(4-chlorophenyl)-2-(4-cyclopentyl(3-pyridyl))-5-methyl-1,3-thiazole
262	4-(4-bromophenyl)-2-(4-cyclopentyl(3-pyridyl))-5-methyl-1,3-thiazole
263	2-(4-cyclopentyl(3-pyridyl))-4-(2-nitrophenyl)-1,3-thiazole
264	4-(2,4-dimethylphenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
265	2-[2-(4-cyclopentyl(3-pyridyl))(1,3-thiazol-4-yl)]-1,4-dimethoxybenzene
266	4-(2H,3H,4H-benzo[b]1,4-dioxepan-7-yl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
267	4-[3,5-bis(trifluoromethyl)phenyl]-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole, C
268	4-[3,5-bis(trifluoromethyl)phenyl]-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, C
269	4-(2H,3H,4H-benzo[b]1,4-dioxepin-7-yl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole
270	2-[4-(methylethyl)(3-pyridyl)]-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
271	1-[2-(4-cyclopentyl(3-pyridyl))(1,3-thiazol-4-yl)]-2-methoxybenzene
272	{4-[2-(4-cyclopentyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy}difluoromethane
273	{4-[2-(4-cyclopentyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy}trifluoromethane
274	2-(4-cyclopentyl(3-pyridyl))-4-(4-nitrophenyl)-1,3-thiazole
275	4-(4-chloro-3-nitrophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
276	2-[4-(methylethyl)(3-pyridyl)]-4-(5-methyl-3-phenylisoxazol-4-yl)-1,3-

Example #	Compound Name
	thiazole
277	4-methoxy-1-{5-methyl-2-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-4-yl)} benzene
278	1-[2-(4-cyclopentyl(3-pyridyl))-5-methyl(1,3-thiazol-4-yl)]-4-methoxybenzene
279	4-(3,4-dichlorophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
280	4-(2,4-dichlorophenyl)-2-(4-cyclopentyl(3-pyridyl))-1,3-thiazole
281	2-(4-cyclopentyl(3-pyridyl))-4-(2-naphthyl)-1,3-thiazole
282	4-(4-chlorophenyl)-2-{4-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl](3-pyridyl)}-1,3-thiazole
283	[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]-N-(4-methylphenyl)carboxamide
284	N-cyclohexyl[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide
285	2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl) morpholin-4-yl ketone
286	[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]-N-benzamide
287	N-(4-methoxyphenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide
288	[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]-N-(4-pyridyl)carboxamide
289	N-bicyclo[2.2.1]hept-2-yl[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide
290	N-(3,4-difluorophenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide, 2,2,2-trifluoroacetic acid
291	N-(3-chloro-4-fluorophenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide, 2,2,2-trifluoroacetic acid
292	4-(4-{[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carbonyl} piperazinyl)benzenecarbonitrile, 2,2,2-trifluoroacetic acid
293	4-(4-chlorophenyl)piperazinyl 2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl) ketone, 2,2,2-trifluoroacetic acid
294	N-(3-cyanophenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide, 2,2,2-trifluoroacetic acid
295	N-(2-furylmethyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide, 2,2,2-trifluoroacetic acid
296	2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl) piperidyl ketone
297	N-(4-fluorophenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide
298	[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]-N-(3-pyridyl)carboxamide

Example #	Compound Name
299	N-(4-chlorophenyl)[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]carboxamide
300	4-[2-(4-phenyl(3-pyridyl))-1,3-thiazol-4-yl]benzenecarbonitrile
301	difluoro {4-[2-(4-phenyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy}methane
302	4-(4-nitrophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
303	4-(4-methylphenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
304	2-(4-phenyl(3-pyridyl))-4-(4-pyrrolidinylphenyl)-1,3-thiazole
305	4-(3-chlorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
306	4-(2-chlorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
307	3-[2-(4-phenyl(3-pyridyl))-1,3-thiazol-4-yl]benzenecarbonitrile
308	4-(3-fluorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
309	4-(2-fluorophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
310	4-(3-nitrophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
311	4-(2-nitrophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
312	4-(3-bromophenyl)-2-(4-phenyl(3-pyridyl))-1,3-thiazole
313	2-(4-phenyl(3-pyridyl))-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
314	4-[4-(methylethyl)(3-pyridyl)]-2-(4-phenyl(3-pyridyl))-1,3-thiazole
315	2-(4-phenyl(3-pyridyl))-4-(3-pyridyl)-1,3-thiazole
316	4-(4-methyl(3-pyridyl))-2-(4-phenyl(3-pyridyl))-1,3-thiazole
317	2-(4-phenyl(3-pyridyl))-4-(2-pyridyl)-1,3-thiazole
318	2-(4-phenyl(3-pyridyl))-4-(4-pyridyl)-1,3-thiazole
319	4-{2-[4-(4-fluorophenyl)-3-pyridyl]-1,3-thiazol-4-yl} benzenecarbonitrile
320	4-(4-fluorophenyl)-2-[4-(4-fluorophenyl)(3-pyridyl)]-1,3-thiazole
321	4-(4-chlorophenyl)-2-[4-(4-fluorophenyl)(3-pyridyl)]-1,3-thiazole
322	2-[4-(4-fluorophenyl)(3-pyridyl)]-4-(4-nitrophenyl)-1,3-thiazole
323	difluoro(4-{2-[4-(4-fluorophenyl)(3-pyridyl)](1,3-thiazol-4-yl)})phenoxy)methane
324	2-[4-(4-fluorophenyl)(3-pyridyl)]-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
325	4-(3-fluorophenyl)-2-[4-(4-fluorophenyl)(3-pyridyl)]-1,3-thiazole
326	4-(3-chlorophenyl)-2-[4-(4-fluorophenyl)(3-pyridyl)]-1,3-thiazole
327	3-{2-[4-(4-fluorophenyl)-3-pyridyl]-1,3-thiazol-4-yl} benzenecarbonitrile
328	4-(3,4-dichlorophenyl)-2-[4-(4-fluorophenyl)(3-pyridyl)]-1,3-thiazole

Example #	Compound Name
329	4-[2-(4-cyclopropyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, hydrogen chloride
330	4-(tert-butyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
331	2-(4-propyl(3-pyridyl))-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
332	4-(2-naphthyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
333	4-(3-chlorophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
334	4-(2-chlorophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
335	4-(4-bromophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
336	4-(3-bromophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
337	4-phenyl-2-(4-propyl(3-pyridyl))-1,3-thiazole
338	4-(4-bromophenyl)-5-methyl-2-(4-propyl(3-pyridyl))-1,3-thiazole
339	trifluoro {4-[2-(4-propyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} methane
340	4-(2,4-dimethylphenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
341	4-(4-phenylphenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
342	3-[2-(4-propyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
343	4-methoxy-1-[2-(4-propyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene
344	4-(2-fluorophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
345	4-(4-fluorophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
346	4-(4-methylphenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
347	difluoro {4-[2-(4-propyl(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy} methane
348	2-methoxy-1-[2-(4-propyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene
349	4-(3-nitrophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
350	4-(2-nitrophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
351	4-(5-methyl-3-phenylisoxazol-4-yl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
352	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzoic acid, N, hydrogen chloride
353	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, 4-methylbenzenesulfonic acid
354	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, methanesulfonic acid
355	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, (1Z)ethene-1,2-dicarboxylic acid
356	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, hydrogen chloride

Example #	Compound Name
357	4-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarboxamidine
358	5-[2-(4-methyl-3-pyridyl)-1,3-thiazol-4-yl]thiophene-2-carbonitrile, 2,2,2-trifluoroacetic acid
359	2-[4-(4-fluorophenyl)(3-pyridyl)]-4-(3-nitrophenyl)-1,3-thiazole
360	4-(2,4-dichlorophenyl)-2-[4-(4-fluorophenyl)(3-pyridyl)]-1,3-thiazole
361	3-[2-(4-propyl-3-pyridyl)-1,3-thiazol-4-yl]phenyl benzoate
362	4-[2-(4-propyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
363	4-(4-nitrophenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
364	4-(4-chlorophenyl)-5-(4-methylphenyl)-2-(4-propyl(3-pyridyl))-1,3-thiazole
365	4-{2-[4-(tert-butyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile
366	3-{2-[4-(tert-butyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile
367	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-fluorophenyl)-1,3-thiazole
368	2-[4-(tert-butyl)(3-pyridyl)]-4-(3-fluorophenyl)-1,3-thiazole
369	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-nitrophenyl)-1,3-thiazole
370	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-chlorophenyl)-1,3-thiazole
371	2-[4-(tert-butyl)(3-pyridyl)]-4-(2-chlorophenyl)-1,3-thiazole
372	2-[4-(tert-butyl)(3-pyridyl)]-4-(3-chlorophenyl)-1,3-thiazole
373	4-(2,4-dichlorophenyl)-2-[4-(tert-butyl)(3-pyridyl)]-1,3-thiazole
374	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-bromophenyl)-1,3-thiazole
375	2-[4-(tert-butyl)(3-pyridyl)]-4-(3-bromophenyl)-1,3-thiazole
376	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-bromophenyl)-5-methyl-1,3-thiazole
377	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-methylphenyl)-1,3-thiazole
378	2-[4-(tert-butyl)(3-pyridyl)]-4-(2,4-dimethylphenyl)-1,3-thiazole
379	2-[4-(tert-butyl)(3-pyridyl)]-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
380	(4-{2-[4-(tert-butyl)(3-pyridyl)](1,3-thiazol-4-yl)}phenoxy)difluoromethane
381	(4-{2-[4-(tert-butyl)(3-pyridyl)](1,3-thiazol-4-yl)}phenoxy)trifluoromethane
382	1-{2-[4-(tert-butyl)(3-pyridyl)](1,3-thiazol-4-yl)}-4-methoxybenzene
383	1-{2-[4-(tert-butyl)(3-pyridyl)](1,3-thiazol-4-yl)}-2-methoxybenzene
384	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-pyrrolidinylphenyl)-1,3-thiazole
385	2-[4-(tert-butyl)(3-pyridyl)]-4-phenyl-1,3-thiazole

Example #	Compound Name
386	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-chloro-3-nitrophenyl)-1,3-thiazole
387	2-[4-(tert-butyl)(3-pyridyl)]-4-(4-methyl(3-pyridyl))-1,3-thiazole
388	[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]-N-piperidylcarboxamide, 2,2,2-trifluoroacetic acid
389	2-[4-(methylethyl)(3-pyridyl)]-4-(3-thienyl)-1,3-thiazole, bromide
390	2-(4-cyclopropyl(3-pyridyl))-4-(3-thienyl)-1,3-thiazole, bromide
391	4-(4-methyl(3-pyridyl))-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
392	2-[4-(methylethyl)(3-pyridyl)]-4-(5,5,8,8-tetramethyl(2-5,6,7,8-tetrahydronaphthyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
393	4-[3-(3,4-dichlorophenyl)isoxazol-5-yl]-2-(4-cyclopropyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
394	2-(4-ethyl(3-pyridyl))-4-(3-thienyl)-1,3-thiazole, bromide
395	4-(3-furyl)-2-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
396	2-(5-bromo(3-pyridyl))-4-(3-fluorophenyl)-1,3-thiazole
397	2-(5-bromo(3-pyridyl))-4-(3-chlorophenyl)-1,3-thiazole
398	4-(2,4-dimethylphenyl)-2-(5-bromo(3-pyridyl))-1,3-thiazole
399	2-[4-(tert-butyl)(3-pyridyl)]-4-(2-bromophenyl)-1,3-thiazole
400	2-[4-(tert-butyl)(3-pyridyl)]-4-(2-nitrophenyl)-1,3-thiazole
401	2-[4-(tert-butyl)(3-pyridyl)]-4-(3-nitrophenyl)-1,3-thiazole
402	4-(3,4-dichlorophenyl)-2-[4-(tert-butyl)(3-pyridyl)]-1,3-thiazole
403	1-{2-[4-(tert-butyl)(3-pyridyl)]-5-methyl(1,3-thiazol-4-yl)}-4-methoxybenzene
404	2-[4-(tert-butyl)(3-pyridyl)]-5-methyl-4-[4-(2-methylpropyl)phenyl]-1,3-thiazole
405	2-[4-(tert-butyl)(3-pyridyl)]-4-(3-chloro-4-methylphenyl)-5-methyl-1,3-thiazole
406	4-(tert-butyl)-2-(5-bromo(3-pyridyl))-1,3-thiazole
407	2-(5-bromo(3-pyridyl))-4-(3-pyridyl)-1,3-thiazole
408	2-[4-(tert-butyl)(3-pyridyl)]-5-methyl-4-phenyl-1,3-thiazole
409	4-(2-{4-[(dimethylamino)methyl]-3-pyridyl}-1,3-thiazol-4-yl)benzenecarbonitrile
410	4-(2-{4-[(4-methylpiperazinyl)methyl]-3-pyridyl}-1,3-thiazol-4-yl)benzenecarbonitrile, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid

Example #	Compound Name
411	4-[2-(4-{{4-(methylethyl)piperazinyl}methyl}-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
412	4-[2-(4-ethyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, methanesulfonic acid
413	4-[2-(4-cyclopropyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile, methanesulfonic acid
414	diethyl{3-[2-(4-methyl(3-pyridyl))(1,3-thiazol-4-yl)]phenyl}amine
415	4-{2-[4-(pyrrolidinylmethyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
416	4-{2-[4-(imidazolylmethyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
417	4-{2-[4-(morpholin-4-ylmethyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
418	4-(2-{4-[(4-(4-pyridyl)piperazinyl)methyl]-3-pyridyl}-1,3-thiazol-4-yl)benzenecarbonitrile, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
419	4-[2-(4-{{(2-methoxyethyl)amino}methyl}-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
420	4-{2-[4-({[2-(dimethylamino)ethyl]amino}methyl)-3-pyridyl]-1,3-thiazol-4-yl}benzenecarbonitrile
421	4-(2-{4-[(methylamino)methyl]-3-pyridyl}-1,3-thiazol-4-yl)benzenecarbonitrile
422	4-(2-{4-[(ethylamino)methyl]-3-pyridyl}-1,3-thiazol-4-yl)benzenecarbonitrile
423	4-[2-(4-{{(methylethyl)amino}methyl}-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
424	2-(2-fluorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
425	2-(3-fluorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
426	3-methoxy-1-[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]benzene, hydrogen chloride
427	2-(2,4-dichlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
428	4-(4-methyl(3-pyridyl))-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole,

Example #	Compound Name
	hydrogen chloride
429	2-(2-chlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
430	2-(3-chlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
431	2-(3-chloro-4-fluorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
432	2-(2,3-dihydrobenzo[b]furan-5-yl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
433	2-(2,3-dichlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
434	4-(4-methyl(3-pyridyl))-2-(4-methylphenyl)-1,3-thiazole, hydrogen chloride
435	2-(3-fluoro-4-methylphenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
436	2-[4-(tert-butyl)phenyl]-4-(4-methyl(3-pyridyl))-1,3-thiazole
437	2-methoxy-1-[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]benzene, hydrogen chloride
438	4-(4-methyl(3-pyridyl))-2-(2-naphthyl)-1,3-thiazole, hydrogen chloride
439	(4-fluorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
440	(4-chlorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
441	(4-methoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
442	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]-3-pyridylamine, hydrogen chloride
443	(2-fluorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
444	(2-chlorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
445	(3-chlorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
446	ethyl 4-{[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]amino} benzoate, hydrogen chloride
447	4-(4-methyl(3-pyridyl))-2-(2-nitrophenyl)-1,3-thiazole, hydrogen chloride
448	4-(4-methyl(3-pyridyl))-2-(3-nitrophenyl)-1,3-thiazole, hydrogen chloride

Example #	Compound Name
449	4-(4-methyl(3-pyridyl))-2-(4-nitrophenyl)-1,3-thiazole, hydrogen chloride
450	(3-fluorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
451	(2-methoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
452	methyl[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]phenylamine, hydrogen chloride
453	dimethyl(4-{[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amino}phenyl)amine, hydrogen chloride
454	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](4-methylphenyl)amine, hydrogen chloride
455	4-chloro-1-{[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]methoxy}benzene, hydrogen chloride
456	4-{[4-(4-methyl(3-pyridyl))-1,3-thiazol-2-yl]amino}benzenecarbonitrile, hydrogen chloride
457	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]phenylamine, hydrogen chloride
458	(3,5-dichlorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
459	4-{[4-(4-methyl(3-pyridyl))-1,3-thiazol-2-yl]amino}benzoic acid, 2,2,2-trifluoroacetic acid
460	2-chloro-1-{[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]methoxy}benzene, 2,2,2-trifluoroacetic acid
461	1-methoxy-4-[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]-2-nitrobenzene, hydrogen chloride
462	2-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
463	4-(4-methyl(3-pyridyl))-2-[3-(trifluoromethyl)phenyl]-1,3-thiazole, hydrogen chloride
464	2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
465	2-isoxazol-5-yl-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
466	4-(4-methyl(3-pyridyl))-2-(4-phenylphenyl)-1,3-thiazole, hydrogen chloride
467	(2,4-dimethoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
468	(2,5-dimethoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride

Example #	Compound Name
469	(3-methoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
470	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](3-methylthiophenyl)amine, hydrogen chloride
471	ethyl 3-[[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]amino}benzoate, hydrogen chloride
472	3-[[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]amino}benzenecarbonitrile, hydrogen chloride
473	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)][4-(phenylmethoxy)phenyl]amine, hydrogen chloride
474	2-(2-chlorophenyl)-5-ethyl-1-[4-(methylethyl)phenyl]imidazole-4-carboxylic acid
475	4-methoxy-1-[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]benzene, hydrogen chloride
476	2-{4-[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]phenoxy}-5-(trifluoromethyl)pyridine, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
477	2-(4-chlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
478	4-{4-[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]phenyl}-1,2,3-thiadiazole, hydrogen chloride
479	2-{4-[(4,5-dichloroimidazolyl)methyl]phenyl}-4-(4-methyl(3-pyridyl))-1,3-thiazole, hydrogen chloride
480	2,4-bis(4-methyl-3-pyridyl)-1,3-thiazole, hydrogen chloride, hydrogen chloride
481	(4-chloro-2-methoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
482	(5-fluoro-2-methylphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
483	(2,4-dichlorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
484	(2,4-difluorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, hydrogen chloride
485	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)][3-(trifluoromethyl)phenyl]amine, hydrogen chloride
486	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)][4-(trifluoromethyl)phenyl]amine, hydrogen chloride
487	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)][2-(trifluoromethyl)phenyl]amine, hydrogen chloride

Example #	Compound Name
488	1-(4-{[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]amino}phenyl)ethan-1-one, hydrogen chloride
489	4-[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile, hydrogen chloride
490	4-[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile
491	2-(4-cyclopropyl(3-pyridyl))-4-(3-nitrophenyl)-1,3-thiazole
492	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](4-nitrophenyl)amine, hydrogen chloride
493	(2-fluorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
494	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]phenylamine
495	methyl[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]phenylamine
496	(4-fluorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
497	2-(2-fluorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole
498	4-(4-methyl(3-pyridyl))-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole
499	2-(2,4-dichlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole
500	2-methoxy-1-[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]benzene
501	4-(4-methyl(3-pyridyl))-2-(2-naphthyl)-1,3-thiazole
502	(4-chlorophenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
503	(4-methoxyphenyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
504	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]-3-pyridylamine
505	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]benzylamine
506	[(4-methoxyphenyl)methyl][4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
507	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)][(4-methylphenyl)methyl]amine
508	[(4-chlorophenyl)methyl][4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
509	(diphenylmethyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
510	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](2-phenylethyl)amine
511	cyclohexyl[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine
512	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](3-morpholin-4-ylpropyl)amine
513	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](2-piperidylethyl)amine
514	butyl[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, 2,2,2-trifluoroacetic acid
515	(2-furylmethyl)[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amine, 2,2,2-

Example #	Compound Name
	trifluoroacetic acid
516	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](oxolan-2-ylmethyl)amine, 2,2,2-trifluoroacetic acid
517	[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)](2-morpholin-4-ylethyl)amine, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
518	dimethyl(3-{[4-(4-methyl(3-pyridyl))(1,3-thiazol-2-yl)]amino}propyl)amine, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid
519	2-(4-chlorophenyl)-5-ethyl-4-(4-propyl(3-pyridyl))-1,3-thiazole
520	2-(4-chlorophenyl)-5-[4-(2-methylpropyl)(3-pyridyl)]-1,3-thiazole
521	5-chloro-2-(4-chlorophenyl)-4-(4-methyl(3-pyridyl))-1,3-thiazole
522	[6-(2,6-difluorophenyl)(3a-hydroimidazolo[1,2-e]pyrimidin-4-yl)](3-methoxyphenyl)amine
523	4-(4-propyl(3-pyridyl))-2-(4-pyridyl)-1,3-thiazole
524	2-(4-nitrophenyl)-4-(4-propyl(3-pyridyl))-1,3-thiazole
525	2-(3-nitrophenyl)-4-(4-propyl(3-pyridyl))-1,3-thiazole
526	4-[4-(4-propyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile
527	2-phenyl-4-(4-propyl(3-pyridyl))-1,3-thiazole
528	2-(4-chlorophenyl)-4-(4-propyl(3-pyridyl))-1,3-thiazole
529	4-(4-propyl(3-pyridyl))-2-(3-thienyl)-1,3-thiazole
530	4-(4-propyl(3-pyridyl))-2-(2-thienyl)-1,3-thiazole
531	2-(5-nitro(3-thienyl))-4-(4-propyl(3-pyridyl))-1,3-thiazole
532	4-(4-propyl(3-pyridyl))-2-pyrazin-2-yl-1,3-thiazole
533	4-(4-propyl(3-pyridyl))-2-[4-(trifluoromethyl)(3-pyridyl)]-1,3-thiazole
534	3-[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile, 2,2,2-trifluoroacetic acid
535	4-[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarboxamidine
536	4-(4-methyl(3-pyridyl))-2-pyrazin-2-yl-1,3-thiazole
537	4-(4-methyl(3-pyridyl))-2-(2-thienyl)-1,3-thiazole
538	4-(5,5,8,8-tetramethyl(2-5,6,7,8-tetrahydronaphthyl))-2-[4-(trifluoromethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
539	4-(4-methyl-3-pyridyl)-1,3-thiazole-2-ylamine, hydrogen chloride
540	4-[4-(4-methyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile, methanesulfonic acid

Example #	Compound Name
541	4-{4-[4-(trifluoromethyl)-3-pyridyl]-1,3-thiazol-2-yl} benzenecarbonitrile
542	2-isoquinolyl-4-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
543	2-(2,6-dichloro(4-pyridyl))-4-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
544	2-(3-chlorophenyl)-4-(4-ethyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
545	2-(3-chlorophenyl)-4-(4-cyclopropyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
546	2-(3-chlorophenyl)-4-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
547	4-(4-cyclopropyl(3-pyridyl))-2-phenyl-1,3-thiazole, 2,2,2-trifluoroacetic acid
548	4-[4-(methylethyl)(3-pyridyl)]-2-phenyl-1,3-thiazole, 2,2,2-trifluoroacetic acid
549	2-(4-chlorophenyl)-4-(4-ethyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
550	2-(4-chlorophenyl)-4-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
551	4-(4-ethyl(3-pyridyl))-2-(3-nitrophenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
552	2-(4-chlorophenyl)-4-(4-cyclopropyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
553	4-(4-cyclopropyl(3-pyridyl))-2-(3-nitrophenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
554	4-[4-(methylethyl)(3-pyridyl)]-2-(3-nitrophenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
555	3-[4-(4-ethyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile, 2,2,2-trifluoroacetic acid
556	3-{4-[4-(methylethyl)-3-pyridyl]-1,3-thiazol-2-yl} benzenecarbonitrile, 2,2,2-trifluoroacetic acid
557	3-[4-(4-cyclopropyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile, 2,2,2-trifluoroacetic acid
558	4-(4-ethyl(3-pyridyl))-2-(4-nitrophenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
559	4-(4-cyclopropyl(3-pyridyl))-2-(4-nitrophenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
560	4-[4-(methylethyl)(3-pyridyl)]-2-(4-nitrophenyl)-1,3-thiazole, 2,2,2-

Example #	Compound Name
	trifluoroacetic acid
561	3-[4-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-2-yl)]-6-methylpyridin-2-ol, 2,2,2-trifluoroacetic acid
562	6-methyl-3-{4-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-2-yl)}pyridin-2-ol, 2,2,2-trifluoroacetic acid
563	4-(4-ethyl(3-pyridyl))-2-(6-methyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
564	4-(4-cyclopropyl(3-pyridyl))-2-(6-methyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
565	2-(6-methyl(3-pyridyl))-4-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
566	4-(4-cyclopropyl(3-pyridyl))-2-(4-methylphenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
567	4-[4-(methylethyl)(3-pyridyl)]-2-(4-methylphenyl)-1,3-thiazole, 2,2,2-trifluoroacetic acid
568	1-[4-(4-cyclopropyl(3-pyridyl))(1,3-thiazol-2-yl)]-4-methoxybenzene, 2,2,2-trifluoroacetic acid
569	4-methoxy-1-{4-[4-(methylethyl)(3-pyridyl)](1,3-thiazol-2-yl)}benzene, 2,2,2-trifluoroacetic acid
570	4-(4-ethyl(3-pyridyl))-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole, 2,2,2-trifluoroacetic acid
571	4-(4-cyclopropyl(3-pyridyl))-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole, 2,2,2-trifluoroacetic acid
572	2-(3-pyridyl)-4,5-dihydrobenzo[e]benzothiazole
573	7-methoxy-2-(3-pyridyl)-4,5-dihydrobenzo[e]benzothiazole
574	8-methoxy-2-(3-pyridyl)-4,5-dihydrobenzo[e]benzothiazole
575	(1R)-6-aza-1,10,10-trimethyl-5-(3-pyridyl)-4-thiatricyclo[7.4.0.0<3,7>]trideca-3(7),5-diene
576	5-[(4-methylphenyl)sulfonyl]-2-(3-pyridyl)-4,5,6,7-tetrahydro-1,3-thiazolo[5,4-c]pyridine
577	2-(4-methyl-3-pyridyl)-4,5-dihydrobenzo[e]benzothiazole
578	2-(3-pyridyl)-4,6,7-trihydro-1,3-thiazolo[4,5-d]pyrimidin-5-one
579	6-methyl-2-(3-pyridyl)-4,6,7-trihydro-1,3-thiazolo[4,5-d]pyrimidin-5-one
580	4-phenyl-2-(3-pyridyl)-2-pyrrolino[2,3-d]1,3-thiazole
581	3-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]pyridin-1-ol
582	3-[4-(4-chlorophenyl)(1,3-thiazol-2-yl)]-4-methylpyridin-1-ol

Example #	Compound Name
583	4-(4-chlorophenyl)-2-(5-methyl(3-pyridyl))-1,3-thiazole
584	2-(3-pyridyl)-4,5,6,7-tetrahydrobenzothiazole
585	2-(4-methyl-3-pyridyl)-4,5,6,7,8-pentahydrocyclohepta[1,2-d]1,3-thiazole
586	2-(3-pyridyl)-4,5,6,7,8-pentahydrocyclohepta[1,2-d]1,3-thiazole
587	1,3-dimethoxy-2-[2-(5-methyl(3-pyridyl))(1,3-thiazol-4-yl)]benzene
588	2-(3-pyridyl)-4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazole
589	2-(4-isoquinolyl)-4-phenyl-1,3-thiazole
590	4-(4-chlorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
591	2-(4-methyl-3-pyridyl)-4,5,6,7-tetrahydrobenzothiazole
592	2-(4-methyl-3-pyridyl)-4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazole
593	2-(4-methyl(3-pyridyl))-4-phenyl-4,5,6,7,8-pentahydrocyclohepta[1,2-d]1,3-thiazole
594	2-[4-(methylethyl)(3-pyridyl)]-4-phenyl-4,5,6,7,8-pentahydrocyclohepta[1,2-d]1,3-thiazole
595	4-phenyl-2-(3-pyridyl)-4,5,6,7,8-pentahydrocyclohepta[1,2-d]1,3-thiazole
596	7-(4-methyl-3-pyridyl)-4,5-dihydro-1,2,5-oxadiazolo[3,4-e]benzothiazole
597	7-(3-pyridyl)-4,5-dihydro-1,2,5-oxadiazolo[3,4-e]benzothiazole
598	2-(4-methyl-3-pyridyl)-6,7-dihydrobenzothiazole-4,5-diimine
599	4-(4-fluorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
600	4-(3-chlorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
601	3-(2-(4-isoquinolyl)-1,3-thiazol-4-yl)benzenecarbonitrile
602	2-(4-isoquinolyl)-4-(3-nitrophenyl)-1,3-thiazole
603	4-(3-fluorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
604	4-(3-bromophenyl)-2-(4-isoquinolyl)-1,3-thiazole
605	4-(4-bromophenyl)-2-(4-isoquinolyl)-1,3-thiazole
606	2-(4-isoquinolyl)-4-(4-nitrophenyl)-1,3-thiazole
607	2-(4-isoquinolyl)-4-(4-methylphenyl)-1,3-thiazole
608	1-(2-(4-isoquinolyl)(1,3-thiazol-4-yl))-4-methoxybenzene
609	difluoro[4-(2-(4-isoquinolyl)(1,3-thiazol-4-yl))phenoxy]methane
610	trifluoro[4-(2-(4-isoquinolyl)(1,3-thiazol-4-yl))phenoxy]methane
611	4-(4-bromophenyl)-2-(4-isoquinolyl)-5-methyl-1,3-thiazole
612	3-aza-4-(3-pyridyl)-5-thiatricyclo[6.2.1.0<2,6>]undeca-2(6),3-diene
613	3-aza-4-(4-methyl(3-pyridyl))-5-thiatricyclo[6.2.1.0<2,6>]undeca-2(6),3-

Example #	Compound Name
	diene
614	3-aza-4-[4-(methylethyl)(3-pyridyl)]-5-thiatricyclo[6.2.1.0<2,6>]undeca-2(6),3-diene
615	4-(2-fluorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
616	4-(2-chlorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
617	1-(2-(4-isoquinolyl)(1,3-thiazol-4-yl))-2-methoxybenzene
618	2-(4-isoquinolyl)-4-(4-phenylphenyl)-1,3-thiazole
619	4-(3,4-dichlorophenyl)-2-(4-isoquinolyl)-1,3-thiazole
620	4-(2,4-dimethylphenyl)-2-(4-isoquinolyl)-1,3-thiazole
621	1-(2-(4-isoquinolyl)(1,3-thiazol-4-yl))-2,4-dimethoxybenzene
622	4-(4-chloro-3-nitrophenyl)-2-(4-isoquinolyl)-1,3-thiazole
623	2-(4-isoquinolyl)-4-(2-naphthyl)-1,3-thiazole
624	4-cyclohexyl-2-(4-isoquinolyl)-1,3-thiazole
625	2-(4-isoquinolyl)-4-(2-nitrophenyl)-1,3-thiazole
626	4-adamantanyl-2-(4-isoquinolyl)-1,3-thiazole
627	4-(3,5-dimethylphenyl)-2-(3-pyridylmethyl)-1,3-thiazole
628	4-phenyl-2-(3-pyridylmethyl)-1,3-thiazole
629	3-methoxy-1-[2-(3-pyridylmethyl)(1,3-thiazol-4-yl)]benzene
630	4-(2-nitrophenyl)-2-(3-pyridylmethyl)-1,3-thiazole
631	4-(3-fluorophenyl)-2-(3-pyridylmethyl)-1,3-thiazole
632	2-pyrazin-2-yl-4-(4-pyridyl)-1,3-thiazole, 2,2-difluoropropanoic acid, 2,2-difluoropropanoic acid, 2,2,2-trifluoroacetic acid, fluoride, fluoride
633	4-(4-fluorophenyl)-2-(1-methylimidazol-5-yl)-1,3-thiazole
634	2-(4-chloro(3-pyridyl))-4-(4-chlorophenyl)-1,3-thiazole, hydrogen chloride
635	4-(4-chlorophenyl)-2-(imidazol-2-ylmethyl)-1,3-thiazole
636	2-(5-bromo(3-pyridyl))-4-(4-fluorophenyl)-1,3-thiazole
637	2-(5-bromo(3-pyridyl))-4-(2-fluorophenyl)-1,3-thiazole
638	2-(5-bromo(3-pyridyl))-4-(3-nitrophenyl)-1,3-thiazole
639	2-(5-bromo(3-pyridyl))-4-(4-chlorophenyl)-1,3-thiazole
640	2-(5-bromo(3-pyridyl))-4-(2-chlorophenyl)-1,3-thiazole
641	4-(3,4-dichlorophenyl)-2-(5-bromo(3-pyridyl))-1,3-thiazole
642	2-(5-bromo(3-pyridyl))-4-(4-bromophenyl)-1,3-thiazole

Example #	Compound Name
643	2-(5-bromo(3-pyridyl))-4-(3-bromophenyl)-1,3-thiazole
644	2-(5-bromo(3-pyridyl))-4-(4-bromophenyl)-5-methyl-1,3-thiazole
645	2-(5-bromo(3-pyridyl))-4-(4-methylphenyl)-1,3-thiazole
646	{4-[2-(5-bromo(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy}difluoromethane
647	{4-[2-(5-bromo(3-pyridyl))(1,3-thiazol-4-yl)]phenoxy}trifluoromethane
648	1-[2-(5-bromo(3-pyridyl))(1,3-thiazol-4-yl)]-4-methoxybenzene
649	4-[2-(5-bromo-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
650	3-[2-(5-bromo-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
651	2-(5-bromo(3-pyridyl))-4-[4-(trifluoromethyl)phenyl]-1,3-thiazole
652	1-[2-(5-bromo(3-pyridyl))(1,3-thiazol-4-yl)]-2-methoxybenzene
653	2-[2-(5-bromo(3-pyridyl))(1,3-thiazol-4-yl)]-1,4-dimethoxybenzene
654	2-(5-bromo(3-pyridyl))-4-(4-phenylphenyl)-1,3-thiazole
655	2-(5-bromo(3-pyridyl))-5-methyl-4-phenyl-1,3-thiazole
656	1-[2-(5-bromo(3-pyridyl))-5-methyl(1,3-thiazol-4-yl)]-4-methoxybenzene
657	2-(5-bromo(3-pyridyl))-4-(4-chloro-3-nitrophenyl)-1,3-thiazole
658	4-(2H,3H,4H-benzo[b]1,4-dioxepan-7-yl)-2-(5-bromo(3-pyridyl))-1,3-thiazole
659	4-[2-(1-hydroxy-4-methyl-3-pyridyl)-1,3-thiazol-4-yl]benzenecarbonitrile
660	4-[4-(1-hydroxy-4-methyl-3-pyridyl)-1,3-thiazol-2-yl]benzenecarbonitrile
661	2-(5-bromo(3-pyridyl))-4-(4-ethyl(3-pyridyl))-1,3-thiazole, 2,2,2-trifluoroacetic acid
662	2-(5-bromo(3-pyridyl))-4-[4-(methylethyl)(3-pyridyl)]-1,3-thiazole, 2,2,2-trifluoroacetic acid
663	2-(5-bromo(3-pyridyl))-4-(5-methyl-3-phenylisoxazol-4-yl)-1,3-thiazole, 2,2,2-trifluoroacetic acid

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

Pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. These salts can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts

and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*).

5 Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as 17 α -hydroxylase-C17,20-lyase inhibitors), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in binding to 17 α -hydroxylase-C17,20-lyase receptors. In general, the compounds of the present invention may be prepared by the methods illustrated in the
10 general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

15 Diseases that can be treated with the compounds of the invention

 The present invention provides a method of inhibiting a lyase, e.g., 17 α -hydroxylase-C17,20 lyase, comprising contacting a lyase with a compound of the invention. The activity can be inhibited by at least 20%, preferably at least about 50%, more preferably at least about 60%, 70%, 80%, 90%, 95%, and most preferably at least about 98%. In one
20 embodiment, the invention provides a method for inhibiting a lyase *in vitro*. In a preferred embodiment, the lyase is *in vivo* or *ex vivo*. For example, the invention provides methods for inhibiting a lyase in a cell, comprising contacting the cell with a compound of the invention, such that the activity of the lyase is inhibited. The cell may further be contacted with a
_____ composition stimulating the uptake of the compound into the cell, e.g., liposomes. In one
25 embodiment, the invention provides a method for inhibiting a lyase in a cell of a subject, comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a formulation comprising a compound of the present invention, such that the lyase is inhibited in a cell of the subject. The subject can be one having a disease associated with a lyase, e.g., cancer. Preferred types of cancer that can be treated
30 according to the invention include prostate cancer and breast cancer. Other diseases that can be treated include diseases in which it is desired to prevent or inhibit the formation of a hormone selected from the group consisting of the androgens testosterone and dihydrotestosterone (DHT) and the estrogens 17 β -estradiol and estrone. Generally, any

disease that can be treated by inhibiting the activity of a lyase, e.g., 17 α -hydroxylase-C17,20-lyase, can be treated with the compounds of the invention.

In general, the invention provides methods and compositions for the treatment of CYP17 metabolite-associated diseases and disorders. Examples include particularly sex
5 steroid hormone dependent cancers, such as androgen-dependent prostate cancer, which may be treated by inhibiting CYP17-mediated androgen synthesis, and estrogen-dependent breast cancer or ovarian cancer, which may be treated by inhibiting CYP17-mediated estrogen synthesis.

For example, adenocarcinoma of the prostate is a common disease that causes
10 significant morbidity and mortality in the adult male population (see Han and Nelson (2000) Expert Opin. Pharmacother. 1: 443-9). Hormonal therapy for prostate cancer is considered when a patient fails with initial curative therapy, such as radical prostatectomy or definitive radiation therapy, or if he is found with an advanced disease. Hormonal agents have been developed to exploit the fact that prostate cancer growth is dependent on androgen. Non-
15 steroidal anti-androgens (NSAAs) block androgen at the cellular level. Castration is another, albeit drastic means of decreasing androgens levels in order to treat or prevent prostate cancer. The methods and compositions of the invention are useful in inhibiting the C17,20-lyase activity of CYP17 and thereby decreasing levels of androgen production and the associated growth of androgen-dependent cancers such as prostate cancer.

20 In another example, breast cancer, particularly breast cancer in postmenopausal women, can be treated by administration of a C17,20-lyase inhibitor of the invention because
adrenal-and-ovarian-androgens-are-the-main-precursors-of-the-estrogens-which-stimulate-the
growth of hormone dependent breast cancer. In addition, breast cancer can be treated with inhibitors of aromatase that prevent interconversion of estrogens and adrenal and ovarian
25 androgens (see Harris et al. (1983) Eur. J. Cancer Clin. Oncol. 19: 11). Patients failing to respond to aromatase inhibitors show elevated levels of androgens in response to aromatase inhibitor treatment (see Harris et al. (1988) Br. J. Cancer 58: 493-6). Accordingly sequential blockade to inhibit androgen production as well as inhibit aromatase may produce greater estrogen suppression and enhanced therapeutic effects in treating breast and other estrogen
30 hormone-dependent forms of cancer. Therefore the inhibitors of the invention may be used alone or in combination with other drugs to treat or prevent hormone-dependent cancers such as breast and prostate cancer.

Furthermore, susceptibility to prostate cancer and breast cancer has been associated with particular polymorphic alleles of the CYP17 gene (see e.g. McKean-Cowdin (2001) Cancer Res. 61: 848-9; Haiman et al. (2001) Cancer Epidemiol. Biomarkers 10: 743-8; Huang et al. (2001) Cancer Res. 59: 4870-5). Accordingly, the compositions of the invention are particularly suited to treating or preventing hormone-dependent cancers in individuals genetically predisposed to such cancers, particularly those predisposed due to an alteration in the CYP17 gene.

Another group of CYP17 metabolite-associated diseases or disorders amenable to treatment with the compositions and methods of the invention include those associated with mineralocorticoid excess such as hypertension caused by sodium retention at renal tubules. Such a mechanism operates in hypertension such as primary hyperaldosteronism and some forms of congenital adrenal hyperplasia. Recently, deficient cortisol metabolism in the aldosterone target organ has been recognized as a novel form of hypertension known as apparent mineralocorticoid excess. Disorders associated with mineralocorticoid synthesis include abnormalities of mineralocorticoid synthesis and/or metabolism which profoundly affect the regulation of electrolyte and water balance and of blood pressure (see e.g. Connell et al. (2001) *Baillieres Best Pract. Res. Clin. Endocrinol. Metab.* 15:43-60). Characteristic changes in extracellular potassium, sodium and hydrogen ion concentrations are usually diagnostic of such disorders. Serious deficiency may be acquired, for example, in Addison's disease, or inherited. In most of the inherited syndromes, the precise molecular changes in specific steroidogenic enzymes have been identified. Mineralocorticoid excess may be caused by aldosterone or 11-deoxycorticosterone by inadequate conversion of cortisol to

cortisone by 11 β -hydroxysteroid dehydrogenase type 2 in target tissues, by glucocorticoid receptor deficiency or by constitutive activation of renal sodium channels. Changes in electrolyte balance and renin as well as the abnormal pattern of corticosteroid metabolism are usually diagnostic. Where these abnormalities are inherited (e.g. 11 β - or 17 α -hydroxylase deficiencies, glucocorticoid remediable hyperaldosteronism (GRA), receptor defects, Liddle's syndrome), the molecular basis is again usually known and, in some cases, may provide the simplest diagnostic tests. Primary aldosteronism, although readily identifiable, presents problems of differential diagnosis, important because optimal treatment is different for each variant. Finally, a significant proportion of patients with essential hypertension show characteristics of mild mineralocorticoid excess, for example low renin levels. As described above, a decrease in CYP17 activity can result in an alteration in

mineralocorticoid (e.g. aldosterone) biosynthesis. Accordingly, the "CYP17 metabolite-associated diseases or disorders" of the invention would include those associated with altered levels of aldosterone production (e.g. hypertension, primary adrenal hyperplasia).

Still other examples of CYP17 metabolite-associated diseases or disorders" are
5 Cushing's disease, prostatic hyperplasia, glucocorticoid deficiency, and endometrial cancer.

The subject that can be treated according to the invention can be a mammal, e.g., a primate, equine, canine, bovine, ovine, porcine, or feline. In preferred embodiments of this method, the mammal is a human. In other embodiments, the invention provides methods for inhibiting the lyase activity of enzymes that are present in organisms other than mammals,
10 e.g., yeast and fungus, e.g., mildew. Certain compounds of the invention may function as antifungal compounds.

Methods of administering the compounds of the invention

The therapeutic methods of the invention generally comprise administering to a
15 subject in need thereof, a pharmaceutically effective amount of a compound of the invention, or a salt, prodrug or composition thereof. The compounds of the invention can be administered in an amount effective to inhibit the activity of a 17 α -hydroxylase-C17,20-lyase. The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable
20 carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally,
including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

Toxicity and therapeutic efficacy of the compounds can be determined by standard
25 pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side
30 effects may be used, care should be taken to design a delivery system that targets such

reagents to the site of affected tissue in order to minimize potential damage to normal cells and, thereby, reduce side effects.

Data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of activity) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. The compounds of the invention have an IC₅₀ less than 10 μ M as determined by the biochemical or cellular assay described herein. Some compounds of the invention are effective at concentrations of 10 nM, 100 nM, or 1 μ M. Based on these numbers, it is possible to derive an appropriate dosage for administration to subjects.

Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound. Such properties include solubility, absorption, biostability and release time (see "*Pharmaceutical Dosage Form and Drug Delivery Systems*" (Sixth Edition), edited by Ansel *et al.*, publ. by Williams & Wilkins, pgs. 27-29, (1995)). Commonly used prodrugs of the disclosed compounds can be designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention.

Major drug biotransformation reactions include *N*-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, *N*-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 11-13, (1996)).

The pharmaceutical compositions can be prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, intraperitoneal, and subcutaneous injections, as well as use of infusion techniques. One or more compounds

of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel *et al.*, publ. by Williams & Wilkins, (1995).

As indicated above, pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically acceptable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin; or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate; or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol; or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate; or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension

by the addition of water provide the compound of the invention in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or

partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

5 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

 Pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water,
10 Ringer's solution and isotonic sodium chloride solution.

 Sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the compound of the invention is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution is then introduced into a water and glycerol mixture and processed to form a
15 microemulsion.

 The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the active compound. In order to maintain such a constant concentration, a continuous
20 intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUSTM model 5400 intravenous pump.

 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or
25 wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or
30 diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of a suppository for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug.

5 Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of the invention can be employed. For purposes of this application, topical
10 application shall include mouth washes and gargles.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage
15 administration will preferably be continuous rather than intermittent throughout the dosage regimen.

The compounds of the invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. The compounds may be administered simultaneously or sequentially. For
20 example, the active compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the active compounds may be useful in combination with agents
~~that are effective in the treatment and prevention of osteoporosis, inflammation,~~
neurofibromatosis, retinosis, and viral infections. The active compounds may also be useful in combination with inhibitors of other components of signaling pathways of cell surface
25 growth factor receptors.

Drugs that can be co-administered to a subject being treated with a compound of the invention include antineoplastic agents selected from vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, or amsacrine. Methods for the safe and
30 effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the

"Physicians' Desk Reference" (PDR), 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA).

5 Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with a compound of the invention to treat a disease, e.g., cancer.

10 When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

Kits of the invention

15 In one embodiment, a compound of the invention, materials and/or reagents required for administering the compounds of the invention may be assembled together in a kit. When the components of the kit are provided in one or more liquid solutions, the liquid solution preferably is an aqueous solution, with a sterile aqueous solution being particularly preferred.

20 The kit may further comprise one or more other drugs, e.g., a chemo- or radiotherapeutic agent. These normally will be a separate formulation, but may be formulated into a single pharmaceutically acceptable composition. The container means may itself be geared for administration, such as an inhalant, syringe, pipette, eye dropper, or ~~other such like apparatus, from which the formulation may be applied to an infected area of~~ the body, such as the lungs, or injected into an animal, or even applied to and mixed with the other components of the kit.

25 The compositions of these kits also may be provided in dried or lyophilized forms. When reagents or components are provided as a dried form, reconstitution generally is by the addition of a suitable solvent. It is envisioned that the solvent also may be provided in another container means. The kits of the invention may also include an instruction sheet defining administration of the agent. Kits may also comprise a compound of the invention, labeled for detecting lyases.

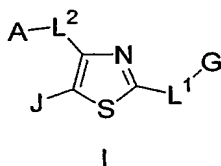
30 The kits of the present invention also will typically include a means for containing the vials in close confinement for commercial sale such as, e.g., injection or blow-molded

plastic containers into which the desired vials are retained. Irrespective of the number or type of containers, the kits of the invention also may comprise, or be packaged with a separate instrument for assisting with the injection/administration or placement of the ultimate complex composition within the body of an animal. Such an instrument may be an inhalant, syringe, pipette, forceps, measured spoon, eye dropper or any such medically approved delivery vehicle. Other instrumentation includes devices that permit the reading or monitoring of reactions or amounts of compounds or polypeptides.

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application) are hereby expressly incorporated by reference.

General Method for the Preparation of Compounds of Formula I.

3-Pyridyl thiazoles of Formula I, wherein A, L¹, J, L² and G are as described in claim 1, are

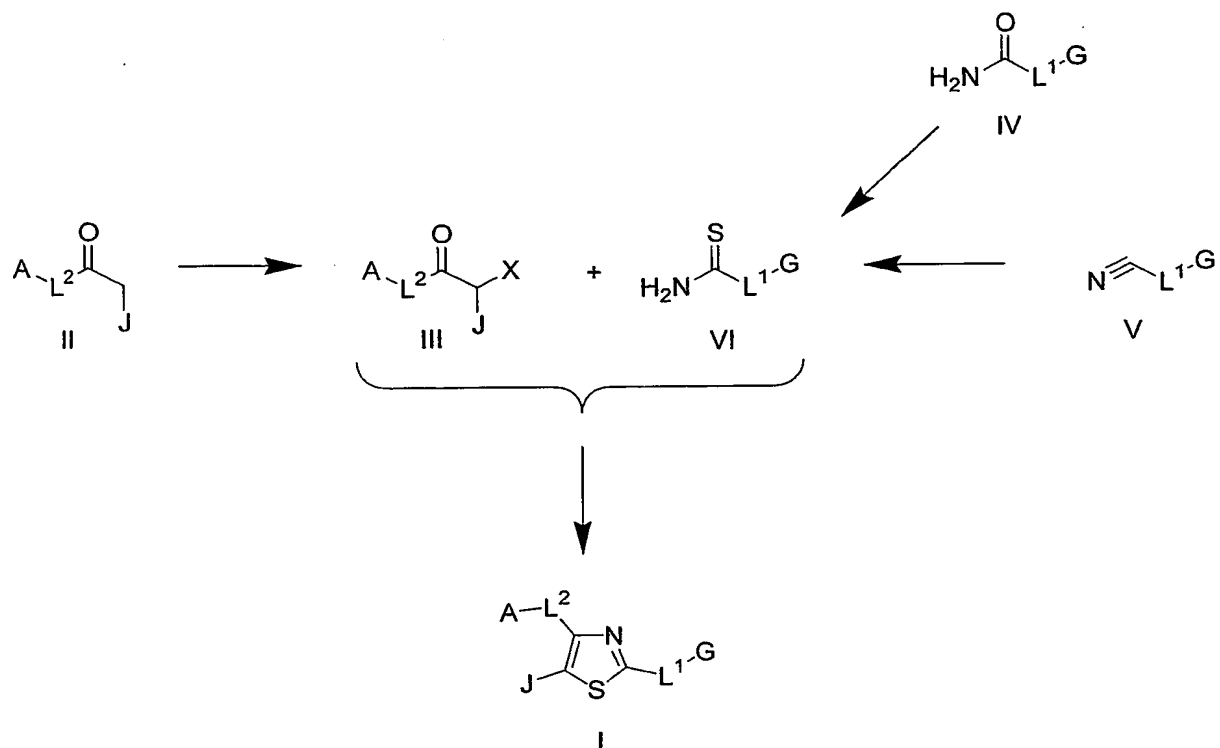


prepared by the general method described below, according to methods described below, or according to methods commonly employed in the art. Compounds of Formula I are prepared

according to Scheme 1, whereby halo ketone III, wherein X is Cl, Br, I, or other leaving group commonly employed in the art, is treated with thioamide VI in a polar solvent, such as an alcoholic solvent, at a temperature between 40 – 120 °C. Preferably the polar solvent is an alcohol such as ethanol, 1-propanol, or 2-propanol. Most preferably, compounds of Formula I are prepared according to General Methods M, N, O, T, U, and V. Alternatively and preferably, compounds of Formula I can be prepared according to Methods G, H, I, J, K, L, P, Q, R, S, and W. Halo ketones III are commercially available or may be prepared using an electrophilic halogen reagent such as bromine, N-chlorosuccinimide, N-bromosuccinimide, or phenyltrimethylammonium tribromide using the general methods or specific examples described below or other methods commonly employed in the art.

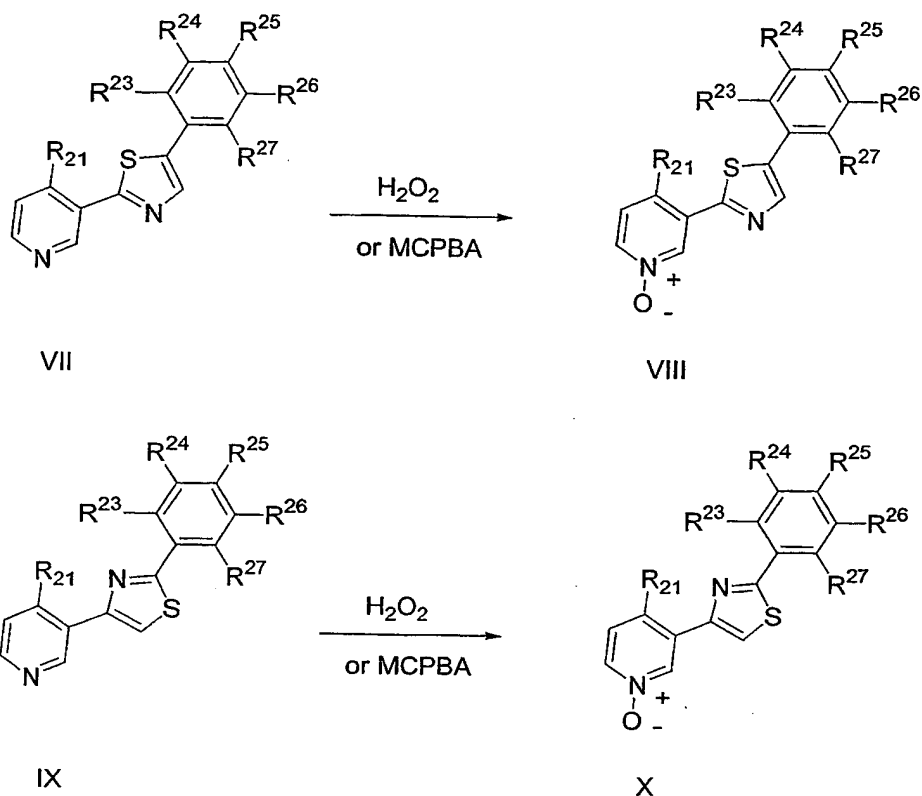
Alternatively, the corresponding alphahydroxy ketone can be converted into III using standard conditions employed in the art to convert an alcohol functionality into a halogen or other leaving group commonly employed in the art. Ketones II are commercially available, are prepared prepared according to methods specifically described below, or are prepared according methods described in the following references: Comins, D. L., Smith, R., Stroud, E., Heterocycles, Vol. 22, No. 2, 1984, 339; Leete, E.; Leete, S. A. S., J. Org. Chem. Vol. 43, No. 11, 1978, 2122; Kim, J. G.; Yu, D. S.; Moon, S. H.; Park, J.; Park, W. W. J. Korean Chem. Soc. Vol. 37, No. 9, 1993, 826. Alternatively, the required ketones II can be prepared from the corresponding carboxylic acids using standard conditions employed in the art to convert a carboxylic acid functionality into a ketone. Thioamide VI can be prepared from nitrile V upon treatment with hydrogen sulphide using procedures described below. Alternatively, VI can be prepared from amide IV upon treatment with Lawessons reagent or P₄S₁₀. Nitriles V are commercially available or can be prepared according to the methods described below for Intermediates A-H, or they can be prepared according the methods described in the following references: Comins, D. L., Smith, R., Stroud, E., Heterocycles, Vol. 22, No. 2, 1984, 339; Leete, E.; Leete, S. A. S., J. Org. Chem. Vol. 43, No. 11, 1978, 2122; Kim, J. G.; Yu, D. S.; Moon, S. H.; Park, J.; Park, W. W. J. Korean Chem. Soc. Vol. 37, No. 9, 1993, 826. Other methods commonly employed in the art may also be used to prepare V. Amides IV are commercially available or they can be prepared by methods commonly employed in the art to prepare amide functionality from carboxylic acid functionality, whereby the requisite carboxylic acid is commercially available or can be prepared according to the following reference: Comins, D. L., Smith, R., Stroud, E., Heterocycles, Vol. 22, No. 2, 1984, 339.

Scheme 1



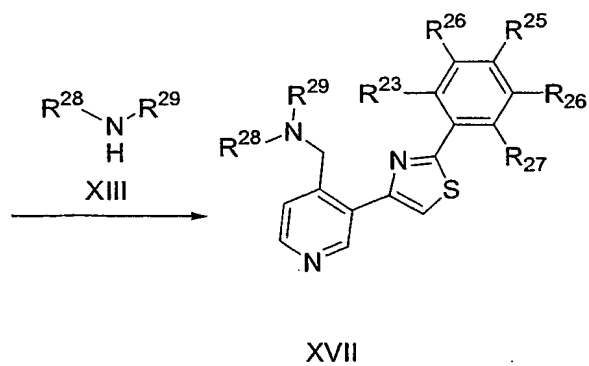
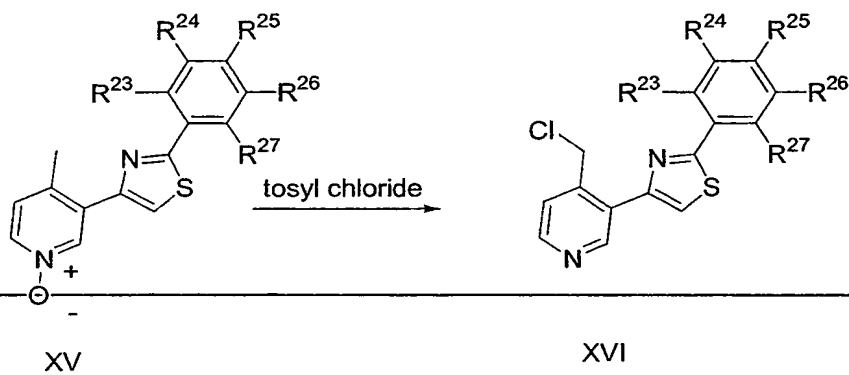
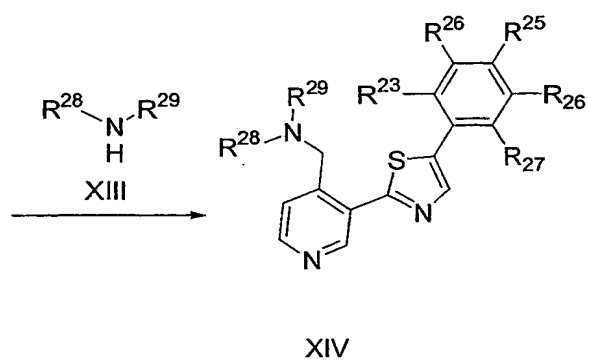
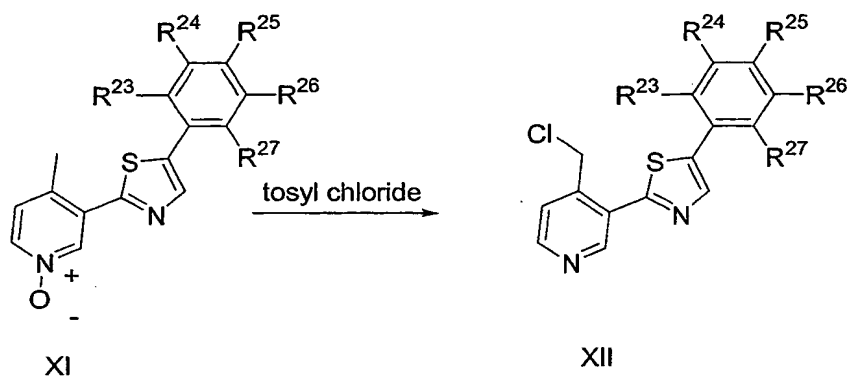
Compounds of Formula I, when A or G is pyridyl, can be converted to an N-oxide upon treatment with a peroxide, such as hydrogen peroxide or MCPBA, in an acidic solvent such as acetic acid, as shown in Scheme 2.

Scheme 2



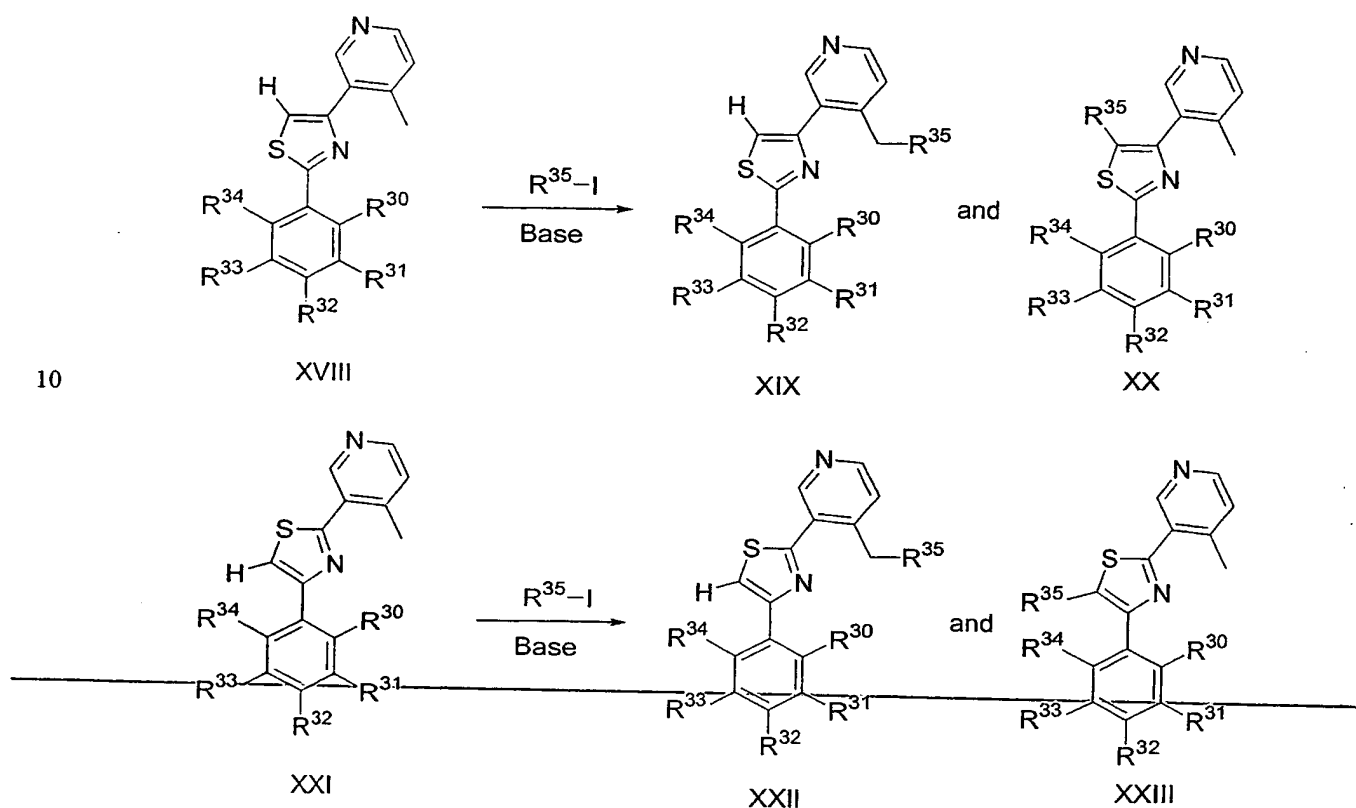
When A or G is 4-methyl pyridyl, such compounds can be treated with H₂O or MCPBA, as shown in Scheme 2, to yield 4-methyl pyridine N-oxides, which can be optionally converted to chloro derivatives XII and XVI as shown in Scheme 3. The N-oxide XI or XV is converted to chloride XII or XVI by treatment with tosyl chloride at elevated temperature. Treatment of chlorides XII or XVI with amines of the formula XIII results in the formation of 4-aminopyridines of the formulae XIV and XVII.

Scheme 3



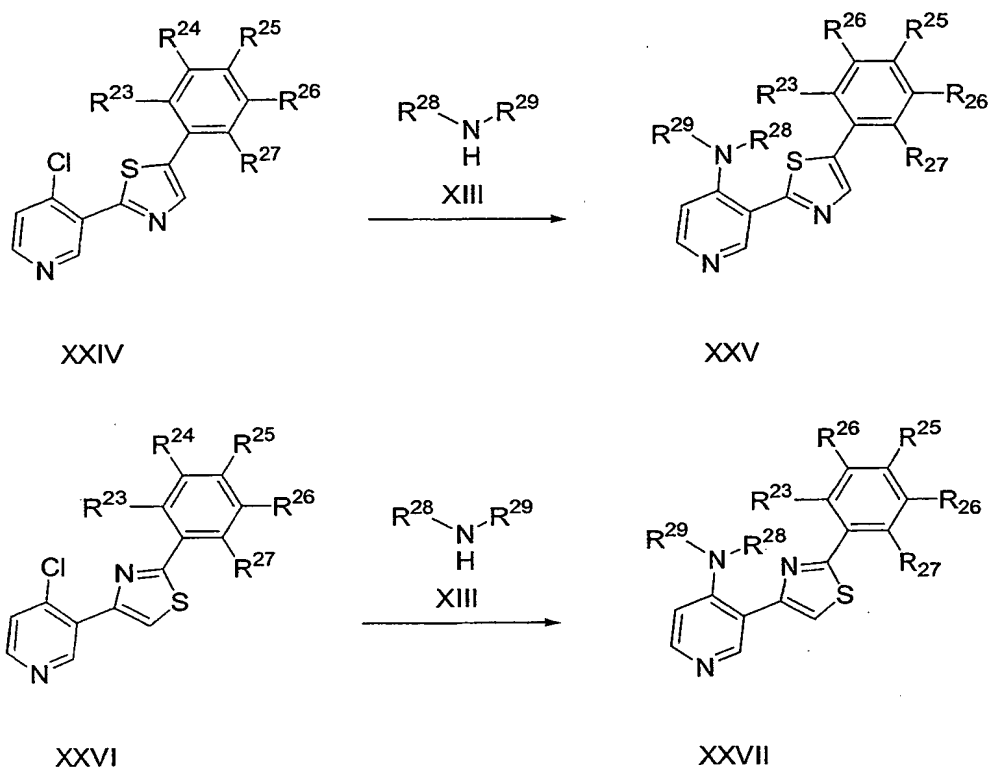
Compounds of Formula I, when A or G is a 4-methyl pyridyl, can be alkylated using a base, such as LDA, followed by treatment with an electrophilic reagent, such as an alkyl iodide, as shown in Scheme 4. Other bases commonly employed in the art, such as *n*-butyl lithium or *tert*-butyl lithium, and other electrophilic reagents commonly employed in the art, such as alkyl bromides, alkyl chlorides, alkyl tosylates, or alkyl triflates, may also be utilized. Separation by chromatography (column chromatography, flash chromatography, preparative TLC, or HPLC) affords the alkylated thiazoles of Formulae XIX and XX.

Scheme 4



Compounds of Formula I, when A or G is a 4-chloropyridyl, can be treated with an amine, as shown in Scheme 5, to form 4-aminopyridines of formulae XXV and XXVII.

Scheme 5



The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application) are hereby expressly incorporated by reference.

Examples

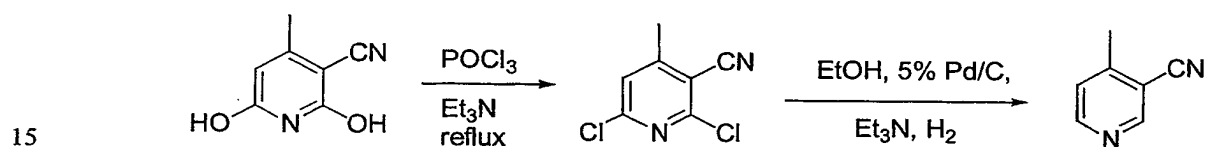
Preparation of the compounds of the invention

General. All reagents are commercially available unless otherwise specified.

Reagents were used as received unless otherwise specified. Proton NMR data is reported downfield from TMS; coupling constants are in hertz. LCMS mass spectral data were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120Å), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the

source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% B over 3.5 min at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 min and a final hold at 95% B of 0.5 min. Total run time was 6.5 min. Purification by HPLC was performed using a Gilson
5 HPLC system (UV/VIS-155 detector, 215 liquid handler, 306 pumps, 819 injection valve and an 811C mixer, the column was a YMC Pro C18 (75 x 30, 5 μ m, 120A); the eluents were A: water with 0.1% TFA, and B: acetonitrile with 0.1% TFA; gradient elution from 10% B to 90% B over 12 min with a final hold at 90% B for 2 min; flowrate was 25 mL per minute. NMR data are in agreement with the structure of all prepared compounds. Elemental
10 analyses were obtained at Robertson Microlit Laboratories, Madison NJ. Melting points are uncorrected.

Preparation of Intermediate A: 4-Methyl-3-cyanopyridine.



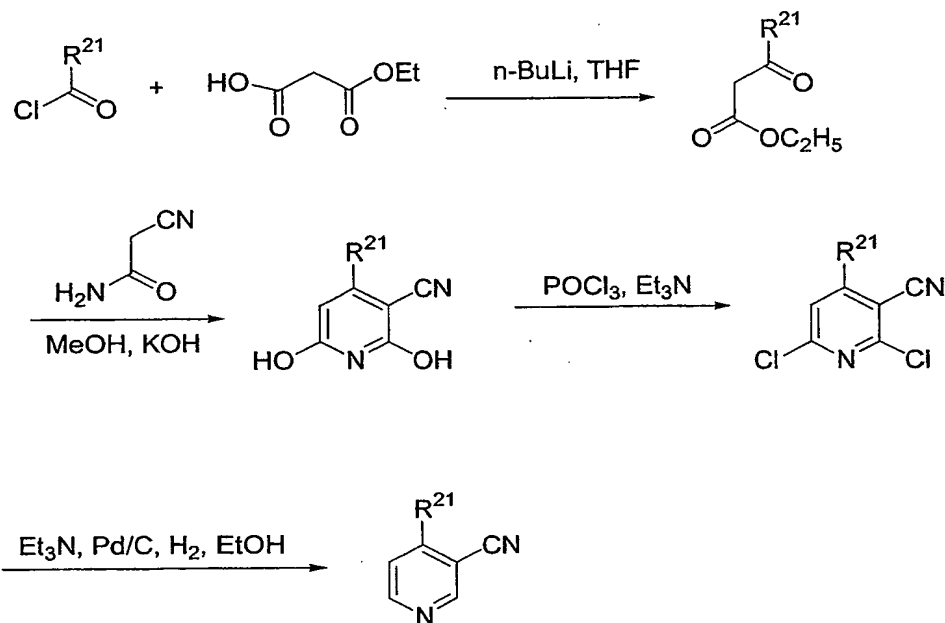
Step 1. 2,6-Dihydroxy-4-methyl-3-pyridinecarbonitrile (150 g, 1 mol) and phosphorus oxychloride (600 mL, 6.4 mol) were stirred under an Ar atmosphere and triethylamine (300 mL, 2.1 mol) was added. After refluxing for 16 h, the mixture was concentrated *in vacuo*, and the residue partitioned between ice water (6 L) and dichloromethane (2 L). The organic
20 phase was washed with aqueous sodium bicarbonate solution, then brine, dried (Na₂SO₄), and then filtered through a pad of silica gel (465 g) on a sintered glass funnel. Elution with dichloromethane and concentration of the filtrate *in vacuo* afforded 109.6 g (58.6%) of 2,6-dichloro-4-methyl-3-cyanopyridine as a colorless crystalline solid, mp 108-110 °C: TLC R_f 0.23 (1:1 hexane-dichloromethane, R_f 0.31 (3:1 hexanes-EtOAc); ¹H NMR (CDCl₃) δ 7.3 (d, 1H), 2.3 (s, 3H); GCMS 187 (M+H⁺).

Step 2. 2,6-Dichloro-4-methyl-3-cyanopyridine (40.8 g, 0.22 mol) was dissolved in anhydrous ethanol (680 mL) and triethylamine (120 mL) by warming, and the solution hydrogenated over 5% palladium on carbon at 10 psi of hydrogen. Upon completion of the reaction, catalyst was removed by filtration. The filtrate was concentrated *in vacuo*. The

resulting solid was triturated with ether, filtered, and then concentrated *in vacuo* to afford 16.3 g (63.1%) of 4-methyl-3-cyanopyridine as colorless needles: mp (40-45 °C, slowly melts); ^1H NMR (CDCl_3) δ 8.8 (s, 1H), 8.5 (d, 1H, $J = 5$ Hz), 7.3 (d, 1H, $J = 5$ Hz), 2.6 (s, 3H); GCMS 118 (M^+).

5

General Method A: Preparation of 4-Substituted-3-cyanopyridines.



10

Step 1. *mono*-Ethyl malonate (35.0 g, 265 mmol) and THF (300 mL) were placed into a 500 mL round-bottomed flask and cooled to -70 °C under Ar. To this solution was added 330 mL of 1.6 M *n*-BuLi (2.0 equiv., 530 mmol) slowly and the solution allowed to stir for 10 min at -70 °C. The acid chloride was added to the solution slowly, stirred for one more h at -70 °C, and then the reaction temperature was allowed to go to rt overnight. The solution was concentrated *in vacuo* and the residue was partitioned between 1N HCl, (200 mL) and Et_2O (2 x 300 mL). The organic layer was washed sequentially with saturated NaHCO_3 solution (200 mL) and H_2O (200 mL), then dried over Na_2SO_4 . The filtrate was concentrated and the crude product was purified by chromatography using hexanes-EtOAc (95:5). The average yields of the beta-ketoesters were 30-50%.

15

Step 2. The beta-ketoester (347 mmol) and 2-cyanoacetamide (347 mmol) were placed into a 500 mL round-bottomed flask and dissolved in 100 mL of THF under Ar. To this solution was slowly added a solution of KOH (1.1 equiv., 25.2 g, 382 mmol) in 150 mL MeOH. The

solution allowed to stir at 70 °C for 8 h, during which time a solid slowly formed. The reaction mixture was cooled the solution to rt and the solid was filtered. The solid was dissolved in warm water (250 mL) and concentrated. HCl was added slowly until the pH was 1 - 2. The resulting solid was filtered and dried to afford the 4-substituted-2,6-dihydroxy-3-cyanopyridine. The average yields of the 4-substituted-2,6-dihydroxy-3-cyanopyridines were 30-90%.

Step 3. In a 500 mL round-bottomed flask were placed the 4-substituted-2,6-dihydroxy-3-cyanopyridine (314 mmol) and POCl₃ (3.3 equiv, 1035 mmol, 95.3 mL) under Ar.

Triethylamine (471 mmol, 65.5mL) was added very slowly using an ice bath for cooling.

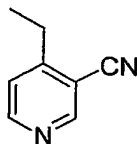
The reaction mixture was heated to 130 °C for 8 h under Ar after the addition was finished. After cooling to rt, the reaction mixture was concentrated *in vacuo* and poured into ice (150 g). The residue was partitioned between CH₂Cl₂ (3 x 200 mL) and ice water. The separated organic layer was washed sequentially with NaHCO₃ (saturated 200 mL) and H₂O (200 mL), then dried over Na₂SO₄. The filtrate was concentrated and purified by column

chromatography using hexanes-EtOAc (80:20) as eluant. The average yields of the 4-substituted-2,6-dichloro-3-cyanopyridines were 35-50%.

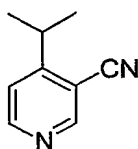
Step 4. Into a 500 mL round-bottomed flask were placed the 4-substituted-2,6-dichloro-3-cyanopyridines (232 mmol), 10% Pd/C (2.0 g), Et₃N (927 mmol, 130 mL) and EtOH (300 mL). The mixture was hydrogenated at atmospheric pressure for 24 to 48 h at rt. The

catalyst was removed by filtration and the filtrate was concentrated. The residue was partitioned between CH₂Cl₂ (3 x 200 mL) and H₂O (200 mL), and then the separated organic layer was dried over Na₂SO₄. Concentration and purification by column chromatography using hexanes-EtOAc (95:5) afforded the 4-substituted-3-cyanopyridines in average yields of 85-95%.

Preparation of Intermediate B: 4-Ethyl-3-cyanopyridine.

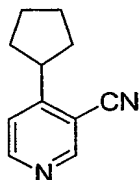


4-Ethyl-3-cyanopyridine was prepared according to General Method A: TLC R_f 0.50 (70:30 hexane-EtOAc); ¹H NMR (CDCl₃) δ 8.80 (d, 1H), 8.62 (d, 1H), 7.26 (dd, 1H), 2.84 (q, 2H), 1.30 (t, 3H); MS 133.1 (M+H⁺).

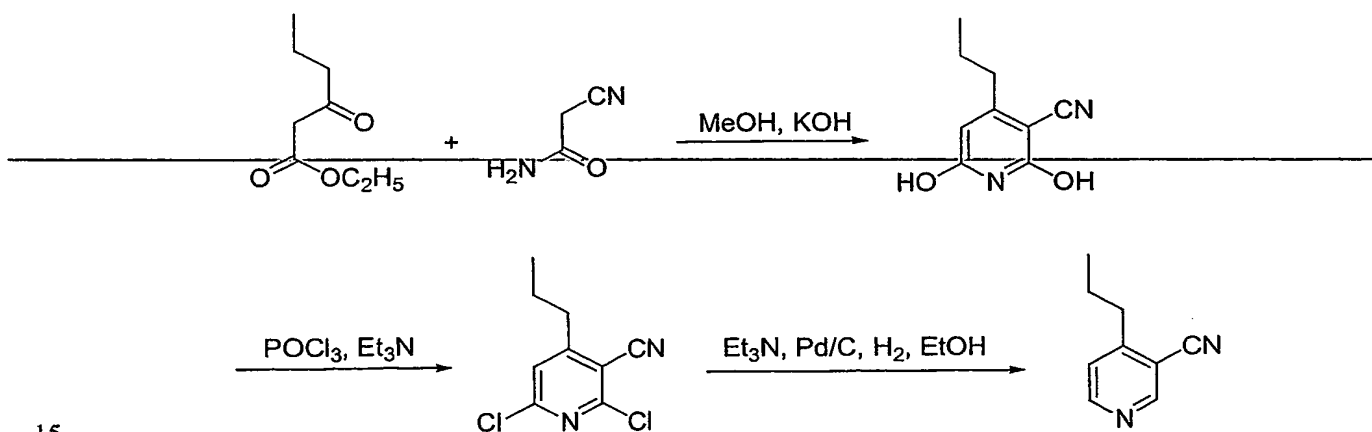
Preparation of Intermediate C: 4-(2-Propyl)-3-cyanopyridine.

4-Propyl-3-cyanopyridine was prepared according to General Method A: TLC R_f 0.40

5 (70:30 hexane-EtOAc); ¹H NMR (CDCl₃) δ 8.80 (d, 1H), 8.75 (d, 1H), 7.26 (dd, 1H), 3.32 (q, 2H), 1.30 (t, 6H); MS 146 (M+H⁺).

Preparation of Intermediate D: 4-(2-Cyclopentyl)-3-cyanopyridine.

10 4-Cyclopentyl-3-cyanopyridine was prepared according to General Method A: TLC R_f 0.70 (70:30 hexane-EtOAc); ¹H NMR (CDCl₃) δ 8.72 (s, 1H), 8.60 (d, 1H), 7.24 (d, 1H), 3.36 (t, 1H), 2.18 (m, 2H), 1.80 (t, 6H); MS 173 (M+H⁺).

Preparation of Intermediate E: 4-(1-Propyl)-3-cyanopyridine.

15

Step 1. Ethyl 3-oxohexanoate (50 g, 0.32 mol) and 2-cyanoacetamide (26.6 g, 0.32 mol) were dissolved in methanol (100 mL). A solution of KOH (20.7 g, 0.37 mol) in methanol (150 mL) was added slowly using an additional funnel. The resulting mixture was refluxed

20 at 70 °C overnight. After the reaction, the white precipitate that formed was filtered and

collected. The crude product was dissolved in warm water (250 mL, 50-60 °C).

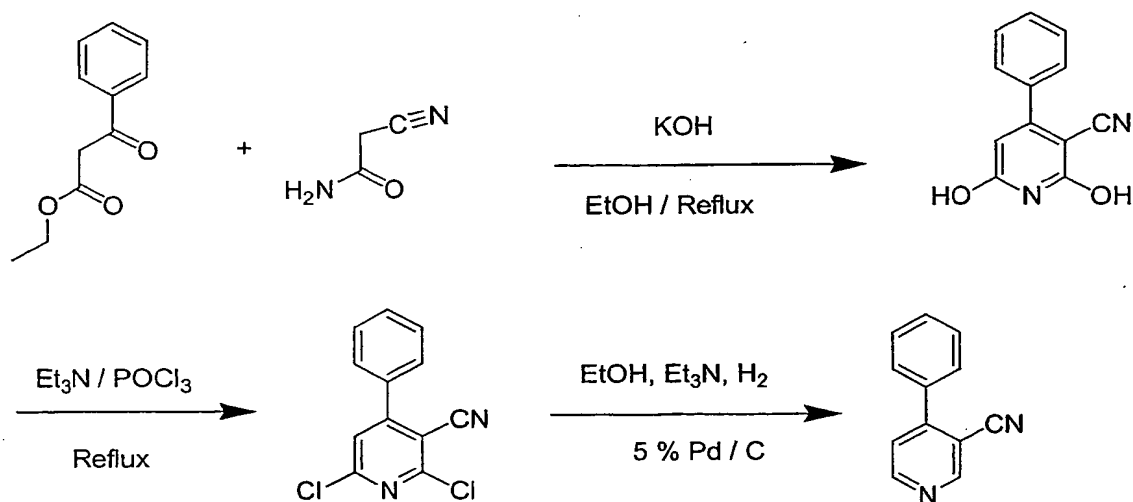
Concentrated HCl was added dropwise with stirring until the pH was 1-2. The white precipitate that formed upon addition of the HCl was filtered and collected, washed with ice water, and dried in a vacuum oven overnight. 2,6-Dihydroxy-4-propyl-3-cyanopyridine

(33.1 g) was produced as a white solid.

Step 2. Under Ar, POCl₃ (56.5 mL, 0.614 mol) was added dropwise into an ice-bath cooled, three-neck round-bottomed flask containing 2,6-dihydroxy-4-propyl-3-pyridinecarbonitrile (33.1 g, 0.186 mol). Then Et₃N (38.86 mL, 0.279 mol) was added into the mixture very slowly with cooling. After the addition was complete, the mixture was warmed to rt, then heated under reflux at 140 °C overnight. After cooling to rt, the excess POCl₃ was evaporated. The brown residue that remained was added slowly into 500 g of crushed ice with stirring. Then concentrated NaOH solution was added dropwise with stirring until the pH reached 8. The aqueous solution was extracted with CH₂Cl₂ (3 x 500 mL). The organic extracts were combined and evaporated to give a brown solid. The crude product was purified by silica gel chromatography using 2% EtOAc/hexane as eluant to give 2,6-dichloro-4-propyl-3-cyanopyridine (24.1 g) as a light yellow solid.

Step 3. 2,6-Dichloro-4-propyl-3-pyridinecarbonitrile (24.1 g, 0.112 mol) and 10% Pd on carbon (3.5 g) were mixed in a 500 mL round-bottomed flask. Denatured EtOH (300 mL) and Et₃N (62.4 mL, 0.448 mol) were then added. The reaction mixture was degassed, filled with Ar, and then degassed again. After this step was repeated 3 more times, H₂ was filled into the flask using a hydrogen balloon. Connected with the hydrogen balloon, the reaction mixture was stirred overnight. After the reaction, the mixture was degassed again. The Pd/C was filtered and the filtrate was evaporated until a light yellow precipitate formed inside.

The turbid filtrate was cooled in the ice bath for about 10 min and then filtered. The filtrate was concentrated and the brownish oil that remained was purified by silica gel chromatography using 20% EtOAc/hexane as eluant. 4-(1-Propyl)-3-cyanopyridine (4.24 g) was produced as light yellow oil in an overall 9.1% yield (3 steps): LCMS t_R = 2.11 min, 147.2 (M+H⁺); ¹H NMR δ 9.00 (s, 1H), 8.50 (d, 1H), 7.33 (d, 1H), 2.84 (t, 2H), 1.77 (m, 2H), 1.00 (t, 3H).

Preparation of Intermediate F: 4-Phenyl-3-cyanopyridine

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Step 1. Ethyl 3-oxo-3-phenylpropanoate (51.9 mL, 0.300 mol) and 2-cyanoacetamide (25.2 g, 0.300 mol) were dissolved in ethanol (100 mL). The mixture was heated to 50 °C under Ar. To this reaction mixture was added a solution of KOH (21.8 g, 0.330 mol) in ethanol (100 mL) via an additional funnel. The reaction was refluxed for approximately 17 h. After

10 cooling to rt, the reaction mixture was filtered. The solid product was washed with ethanol and dried *in vacuo* overnight at 45 °C, providing 12.5 g (19.6%) of 2,6-dihydroxy-4-phenyl-3-cyanopyridine as a white solid.

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Step 2. 2,6-Dihydroxy-4-phenyl-3-cyanopyridine (6.0 g, 28.2 mmol) and triethylamine (4.2 mL, 30.6 mmol) were charged together into a round-bottomed flask. To this via syringe was added phosphorus oxychloride (8.2 mL, 90.4 mmol). The reaction mixture was refluxed for

15

17 h under Ar, then concentrated to an oil under reduced pressure to remove excess POCl₃. This oil was then poured slowly into a beaker with ice-water. The brown precipitate that formed was filtered, washed with copious amounts of water, then dried *in vacuo* overnight at 45 °C. The solid was purified by silica gel chromatography (mobile phase

20 dichloromethane), providing 3.83 g (54.5%) of 2,6-dichloro-4-phenyl-3-cyanopyridine as an off-white solid.

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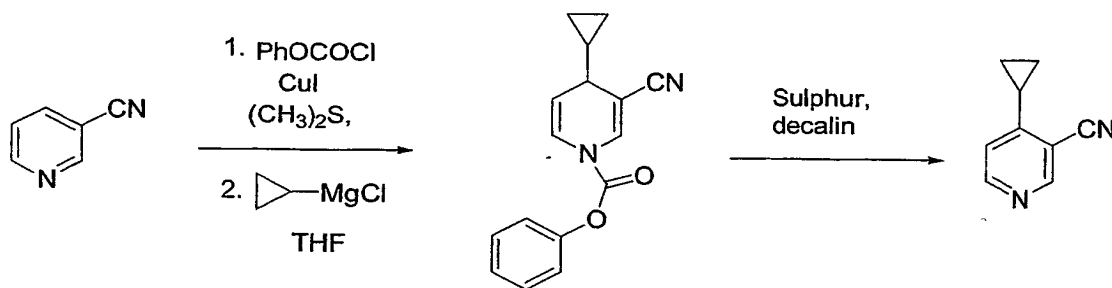
Step 3. Into a dry round-bottomed flask was charged 5% palladium on carbon (0.38 g) and anhydrous ethanol (5 mL). Into another flask was charged 2,6-dichloro-4-phenyl-3-cyanopyridine (3.83 g, 15.4 mmol), triethylamine (8.57 mL, 61.5 mmol) and anhydrous

25 ethanol (80 mL). This solution was transferred to the reaction flask and this flask was then purged with Ar. The flask was evacuated and then purged with Ar; this process was

25

repeated twice more. A balloon of H_2 was attached to the flask and the reaction was then purged with hydrogen, then evacuated. The H_2 was released into the reaction flask and the reaction mixture was hydrogenated for 48 h. The reaction mixture was filtered and washed with ethanol. The filtrate was concentrated and the resulting oil was purified by column chromatography (mobile phase 20% EtOAc/hexane), providing 2.0 g (72%) of 4-phenyl-3-cyanopyridine as a white solid. TLC R_f = 0.1618 (20% EtOAc/Hex); 1H NMR (CD_2Cl_2) δ 7.50 (d, 1H, J = 5.3 Hz) 7.58-7.55 (m, 3H), 7.63-7.62 (m, 3H), 8.80 (d, 1H, J = 5.3 Hz), 8.94 (s, 1H); GCMS m/z 180 (M^+), t_R = 8.0 min.

10 Preparation of Intermediate G: 4-Cyclopropyl-3-cyanopyridine



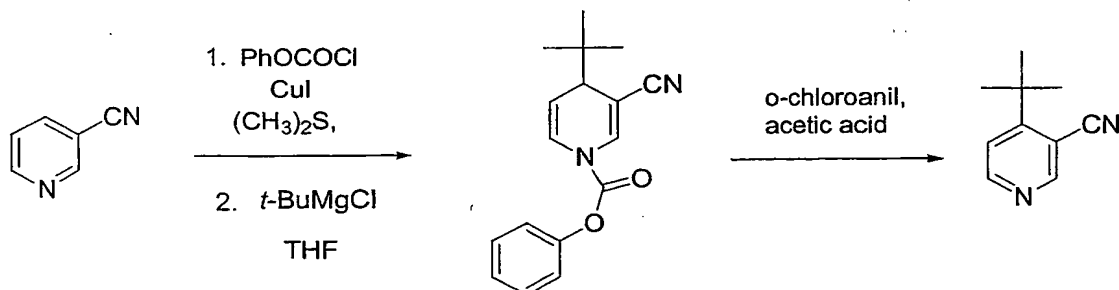
Step 1. To a mixture of CuI (1.37, 0.0072 mol), dimethyl sulphide (33.5 mL, 0.46 mol) and 3-cyanopyridine (15.0g, 0.144 mol) in anhydrous THF (390 mL) at -25 to -20 $^{\circ}C$ was added phenyl chloroformate (23.9 mL, 0.19 mol) and the mixture was stirred at this temperature for 15-20 min. To this suspension at -25 to -20 $^{\circ}C$ was added cyclopropyl magnesium bromide (126 mL, 0.173 mol) over 20-30 min. The mixture was stirred at -25 to -20 $^{\circ}C$ for 15 min, then warmed slowly to rt over 45-50 min. The reaction mixture was quenched with 20% NH_4Cl (105 mL), followed by extraction of the aqueous layer with diethyl ether (300 mL). The organic layer was washed sequentially with an aqueous solution of 1:1 20% NH_4Cl / NH_4OH (2 x 45 mL), water (75 mL), 10% HCl (2 x 75 mL), water (75 mL) and brine (125 mL), then dried over anhydrous Na_2SO_4 . The solution was concentrated to dryness to give the crude 3-cyano-4-cyclopropyl-1-phenoxycarbonyl-1,4-dihydropyridine.

Step 2. A mixture of the crude dihydropyridine and sulphur (3.9g, 0.144 mol) was heated in decalin (250 mL) for a period of 3 h. The reaction mixture was cooled to rt and vacuum distilled to give 1.73g (8.5%) of 4-cyclopropyl-3-cyanopyridine: R_f 0.24 (25%

EtOAc/hexane); LCMS t_R = 1.50 min, 145.10 ($M+H^+$); 1H NMR ($CDCl_3$) δ 8.75 (1H, s), 8.60 (1H, d), 6.80 (1H, d), 2.30 (1H, m), 1.32 (2H, m), 0.97 (2H, m).

Preparation of Intermediate H: 4-(*tert*-Butyl)-3-cyanopyridine

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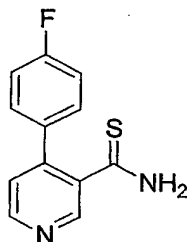


Step 1. In a 2000 mL, three-necked flask equipped with an overhead stirrer were placed 3-cyanopyridine (20.8 g, 0.2 mol), CuI (1.9 g, 0.01 mol), methyl sulfide (48 mL), and 600 mL of THF under Ar. The solution was cooled to -40 °C and phenylchloroformate (25.1 mL, 0.2 mol) was added via an additional funnel with stirring. After 25 min, 0.1 M solution of *tert*-butylmagnesium chloride in THF (200 mL, 0.2 mol) was added dropwise over 1h. The mixture was stirred at -40 °C for 2 h, then at rt overnight. Aqueous 20% NH₄Cl (300 mL) and Ether (400 mL) was added into the mixture. After stirring for 5 min, the organic layer was collected and then washed sequentially with 200 mL of NH₄Cl/ NH₄OH (50/50) twice, 200 mL of water once, 200 mL of 10% HCl twice, 200 mL of water once, and then 200 mL of brine once. After drying over MgSO₄, the solution was filtered and concentrated to yield a brown oil. The crude product was purified by silica gel chromatography (10% EtOAc/hexane) to give 10.0 g of the intermediate dihydropyridine as a brown oil.

Step 2. The intermediate dihydropyridine (10.0 g) was dissolved in dry toluene (100 mL). A solution of *o*-chloroanil (12.3 g, 0.5 mol) in 70 mL of acetic acid was added dropwise. The mixture was stirred at rt for 8 h and then concentrated. Toluene (100 mL), ether (100 mL), celite (10 g), and 10% NaOH solution (200 mL) were then added. The mixture was stirred for 15 min and filtered through celite. The dark organic layer was washed with 100 mL portions of 10% NaOH and water, then extracted with 10% HCl (4 x 100 mL). The combined organic extracts were concentrated to approximately 100 mL, cooled, made basic with 20% NaOH, and then extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layer was washed with brine, dried with K₂CO₃, and then concentrated to yield 3.8 g of 4-(*tert*-

butyl)-3-cyanopyridine as a yellow oil (overall yield is 11.9%): LCMS t_R = 2.23 min, 161.2 ($M+H^+$); 1H NMR 8.80 (s, 1H), 8.65 (d, 1H), 7.40 (d, 1H), 1.50 (s, 9H).

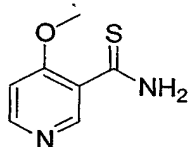
Preparation of Intermediate I: 4-(4-Fluorophenyl)-3-cyanopyridine



- 5 4-(4-Fluorophenyl)-3-cyanopyridine was prepared according to the method described for Intermediate H from 3-pyridinecarbonitrile (3.12 g, 0.03 mol), providing 1.08 g (overall yield 18.2%) of 4-(4-fluorophenyl)-3-cyanopyridine as a white solid: LCMS t_R = 2.33 min, 199.3 ($M+H^+$).

Preparation of Intermediate J: 4-Methoxy-3-cyanopyridine

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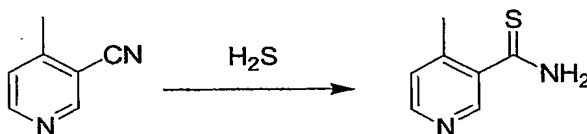
- Step 1. A stirred mixture of (1-ethoxylidene)malononitrile (50 g, 0.36 mol), dimethylformamide dimethyl acetal (84.9 mL, 0.6 mol) and anhydrous methanol (110 mL)
15 was refluxed under Ar for 1 h, then left to cool and stand at rt overnight. After concentration ~~in vacuo~~, the resulting solid was triturated with ice-cold methanol, filtered, and then dried to afford 41.78 g (65.5%) of 1,1-dicyano-2-methoxy-4-dimethylamino-1,3-butadiene as reddish-pink crystals, mp 131-132 °C; TLC R_f 0.24 (dichloromethane), R_f 0.31 (2:1 hexane-acetone); 1H NMR (CD_2Cl_2) δ 7.6 δ (d, 1H), 5.1 (d, 1H), 4.1 (s, 3 H), 3.2 (s, 3H), 2.9 (s,
20 3H); LCMS 178 ($M+H^+$).

- Step 2. Hydrogen chloride gas was vigorously bubbled into a stirred suspension of 1,1-dicyano-2-methoxy-4-dimethylamino-1,3-butadiene (8.29 g, 46.8 mmol) in anhydrous methanol (178 mL) for 5 min periods twice during the day, then left to stir at rt over the weekend. The yellow solution was concentrated *in vacuo*, and the resulting solid stirred in
25 methanol while sodium bicarbonate was cautiously added until gas evolution ceased, and the pinkish-red liquid was basic to pH paper. The reaction mixture was concentrated to a solid,

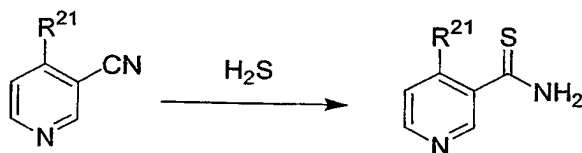
trituated with dichloromethane, and then filtered. The filtrate was concentrated *in vacuo* to afford 2-chloro-3-cyano-4-methoxypyridine as a pink solid (7.0 g, 89%). The product could be recrystallized from methanol as fine, pastel yellow needles, mp 168.5–171 °C: ¹H NMR (CDCl₃) δ 8.4 (d, 1H), 6.9 (d, 1H), 4.0 (s, 3 H); LCMS 169 (M+H⁺). Anal. Calcd for C₇H₅ClN₂O: C, 49.87; H, 2.99; N, 16.62; Cl, 21.03. Found: C, 49.87; H, 2.97; N, 16.63; Cl, 20.95.

Step 3. A solution of 2-chloro-3-cyano-4-methoxypyridine (3.4 g, 20.0 mmol) in anhydrous ethanol (75 mL) was hydrogenated over 5% Pd/C (340 mg) at 10 psi. Upon completion of the reaction, catalyst was removed by filtration. The filtrate was *in vacuo* to afford 2.54 g (94.7%) of 4-methoxy-3-cyanopyridine as a colorless solid. A sample was recrystallized from dichloromethane/hexane, mp 124.5–126 °C (colorless needles): TLC R_f 0.2 (2% methanol/dichloromethane); TLC R_f 0.1 (1:1/ hexane:EtOAc); ¹H NMR (CDCl₃) δ 8.7 (s, 1H), 8.6 (d, 1H), 6.9 (d, 1H), 4.0 (s, 3H); GCMS 134 (M⁺). Anal. Calcd for C₇H₆N₂O: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.43; H, 4.48; N, 20.75.

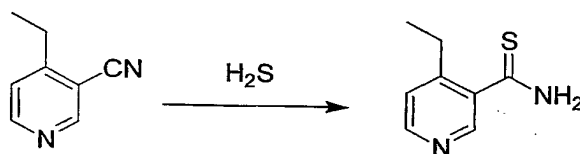
Preparation of Intermediate K: 4-Methylpyridine-3-thiocarboxamide



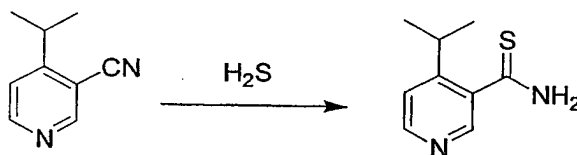
Hydrogen sulfide gas was bubbled into a solution of 4-methyl-3-cyanopyridine (40.8 g, 0.346-mol) in absolute ethanol (680 mL) and triethylamine (0.33 mol) with ice cooling for 1 h. The reaction mixture was stirred overnight and then the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (500 mL) and the solution was heated at 50–55 °C for 4.0–4.5 h, then allowed to cool to rt. The mixture was filtered, the solid was trituated and washed with more EtOAc, and then filtered. The filtrate was concentrated *in vacuo* to afford crude product. The crude was purified by taking it back up into dichloromethane (100 mL), heating the mixture to reflux, then allowing it to cool with stirring. The solid was filtered, washed with dichloromethane, and then dried to afford 24.1 g (72%) of 4-methylpyridine-3-thiocarboxamide as a sand-colored solid, mp 104.5–106 °C: TLC R_f 0.08 (5% methanol/dichloromethane); TLC R_f 0.18 (EtOAc); ¹H NMR (DMSO-*d*₆) δ 10.1 (broad s, 1H), 9.6 (broad s, 1H), 8.4 (d, 1H), 8.3 (s, 1H), 7.2 (d, 1H), 2.3 (s, 3H); LCMS 153 (M+H⁺).

General Method B: Preparation of 4-Substituted Pyridine-3-thiocarboxamides

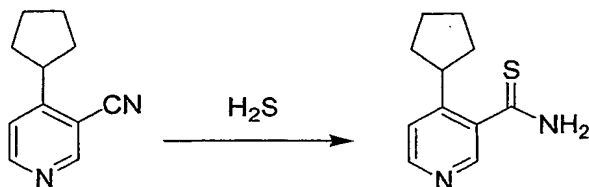
Hydrogen sulfide was bubbled for 30 min into a solution containing the 4-alkyl-3-cyanopyridines (178 mmol) in DMF (300 mL). Diethylamine (1.5 eq) was added and the mixture was heated at 60 °C for 1 h. The reaction mixture was concentrated and the residue was partitioned between CH₂Cl₂ (3 x 200 mL) and H₂O (200 mL). The organic layer was dried (Na₂SO₄) and purified by column chromatography using 60:40 hexanes-EtOAc to afford the pyridine thiocarboxamides. The average yield was 80-95%.

Preparation of Intermediate L: 4-Ethylpyridine-3-thiocarboxamide

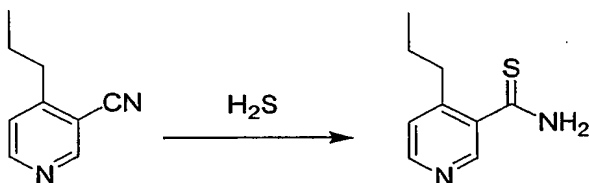
4-Ethylpyridine-3-thiocarboxamide was prepared according to General Method B: TLC R_f 0.55 (EtOAc); LCMS 167.1 (M+H⁺); ¹H NMR (CDCl₃) δ 8.50 (s, 1H), 8.46 (d, 2H), 7.96 (bs, 1H), 7.66 (bs, 1H), 2.86 (q, 2H), 1.30 (t, 3H).

Preparation of Intermediate M: 4-(2-Propyl)pyridine-3-thiocarboxamide

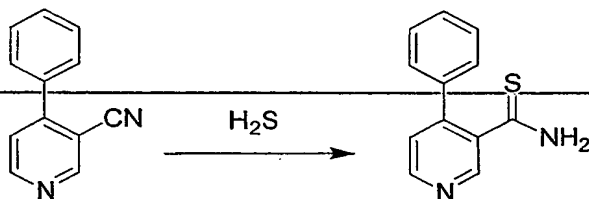
4-(2-Propyl)pyridine-3-thiocarboxamide was prepared according to General Method B: TLC R_f 0.10 (50% EtOAc/hexanes); LCMS 181 (M+H⁺); ¹H NMR (CDCl₃) δ 8.48 (d, 1H), 7.24 (s, 1H), 7.20 (d, 1H), 3.46 (m, 1H), 1.26 (d, 6H).

Preparation of Intermediate N: 4-(2-Cyclopentyl)pyridine-3-thiocarboxamide

5 4-(Cyclopentyl)pyridine-3-thiocarboxamide was prepared according to General Method B: TLC R_f 0.30 (60/40 hexanes/EtOAc); LCMS 206.8 (M+H⁺); ¹H NMR (CDCl₃) δ 8.75 (s, 1H), 8.40 (d, 2H), 7.30 (d, 1H), 3.38 (t, 1H), 2.08 (m, 2H); 1.70 (m, 6H).

Preparation of Intermediate O: 4-(1-Propyl)pyridine-3-thiocarboxamide

4-(1-Propyl)pyridine-3-thiocarboxamide was prepared according to General Method B: LCMS t_R = 1.05 min, 181.1 (M+H⁺); ¹H NMR (CDCl₃) δ 8.05 (s, 1H), 8.00 (d, 1H), 7.15 (d, 1H), 2.80 (t, 2H), 1.66 (m, 2H); 0.98 (t, 3H).

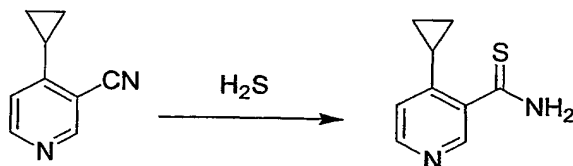
Preparation of Intermediate P: 4-Phenylpyridine-3-thiocarboxamide

20 4-Phenyl-3-cyanopyridine (2.0 g, 11 mmol) was dissolved into DMF (40 mL). The reaction flask was attached to a scrubber (bleach). The reaction was cooled in an ice-water bath and hydrogen sulfide (excess) was bubbled in via needle for 40 min. To the mixture was added diethylamine (1.72 mL, 16.6 mmol). The mixture was heated to 60 °C for 45 min. The reaction was then concentrated under reduced pressure and purified by column
 25 chromatography (mobile phase 30% EtOAc/hexane to 60% EtOAc/hexane). This yielded 1.85 g (77.8%) of 4-phenylpyridine-3-thiocarboxamide as a yellow solid:

TLC R_f 0.05 (40% EtOAc/hexanes); $t_R = 1.37$; ^1H NMR (CDCl_3) δ 6.57-6.50 (m, 2H), 7.45-7.44 (m, 4H), 7.52 (m, 2H), 8.63 (d, 1H), 9.01 (s, 1H); LCMS (ES) m/z 215.1 ($\text{M}+\text{H}^+$).

Preparation of Intermediate Q: 4-Cyclopropylpyridine-3-thiocarboxamide

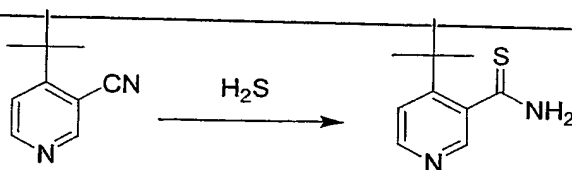
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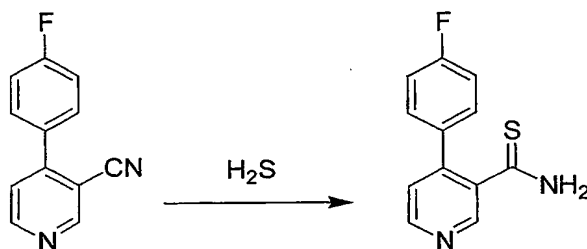
To a solution of 4-cyclopropyl-3-cyanopyridine (4.83 g, 34 mmol) in absolute ethanol (100 mL) upon cooling, was purged hydrogen sulphide gas for a period of 1 h. To this solution
 10 was added diethylamine (5.3 mL, 51 mmol) and the mixture was heated to 50-55 °C for a period of 4.0-4.5 h. The reaction mixture was then stirred for 16-18 h at rt in order to consume the remaining amount of starting material. The reaction mixture was
 Concentrated *in vacuo* and subjected to silica gel chromatography using 20-100% EtOAc-hexane to yield 5.01 g (82%) of 4-cyclopropylpyridine-3-thiocarboxamide: LCMS $t_R = 0.70$
 15 min, 179 ($\text{M}+\text{H}^+$); ^1H NMR ($\text{DMSO}-d_6$) δ 10.21 (br s, 1H), 9.75 (br s, 1H), 8.32 (d, 1H), 8.26 (s, 1H), 6.83 (d, 1H), 2.12 (m, 1H), 1.04 (m, 2H), 0.80 (m, 2H).

Preparation of Intermediate R: 4-(*tert*-Butyl)pyridine-3-thiocarboxamide

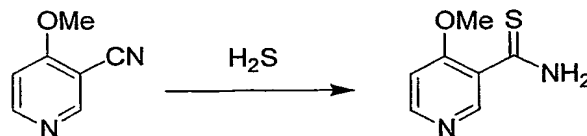
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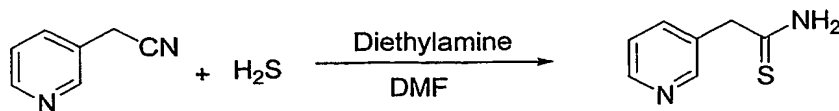
4-(*tert*-Butyl)pyridine-3-thiocarboxamide was prepared according to General Method B: LCMS $t_R = 0.91$ min, 195.2 ($\text{M}+\text{H}^+$); ^1H NMR (CDCl_3) δ 8.38 (d, 1H), 8.26 (s, 1H), 8.00 (br s, 1H), 7.60 (br s, 1H), 7.35 (d, 1H); 1.50 (s, 9H).

Preparation of Intermediate S: 4-(4-Fluorophenyl)pyridine-3-thiocarboxamide

4-(4-Fluorophenyl)pyridine-3-thiocarboxamide was prepared according to General Method B: LCMS $t_R = 1.52$ min, 233.2 ($\text{M}+\text{H}^+$).

5 Preparation of Intermediate T: 4-Methoxypyridine-3-thiocarboxamide

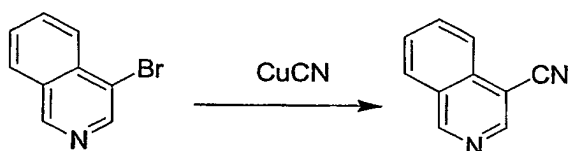
Hydrogen sulfide gas bubbled into a solution of 3-cyano-4-methoxypyridine (14.7 g, 87.1 mmol) in absolute ethanol (270 mL) and triethylamine (130 mmol) with ice cooling for 1 h. The reaction mixture was stirred overnight and then the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (200 mL) and heated at 50-55 °C for 4.0-4.5 h, then allowed to cool to rt. The mixture was filtered, and the solid was triturated with more EtOAc and then filtered. The filtrate was concentrated *in vacuo* to afford the crude product. This was purified by taking it back up into dichloromethane (75 mL), heating the mixture to reflux, then allowing it to cool with stirring. The solid was filtered, washed with dichloromethane, and then dried to afford 9.6 g (65.3%) of 4-methoxypyridine-3-thiocarboxamide as a pale yellow solid: TLC R_f 0.21 (5% methanol/dichloromethane); TLC R_f 0.12 (EtOAc); ^1H NMR ($\text{DMSO}-d_6$) δ 10.1 (broad s, 1H), 9.4 (broad s, 1H), 8.6 (s, 1H), 8.4 (d, 1H), 7.1 (d, 1H), 3.9 (s, 3H); LCMS 153 ($\text{M}+\text{H}^+$).

20 Preparation of Intermediate U: 2-(3-Pyridyl)thioacetamide

Hydrogen sulfide gas was bubbled into a solution of 6.0 g (51 mmol) of 3-pyridylacetonitrile in 100 mL anhydrous DMF under Ar at rt at a moderate rate for 20 min. The reaction was

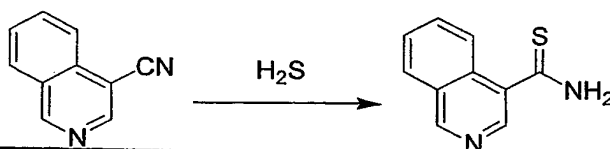
warmed to 60 °C, then a solution of diethylamine (7.88 mL, 76.5 mmol) in 10 mL DMF was added in one portion. After 1.5 h, the reaction mixture was cooled and Ar was bubbled through the reaction for 1 h. The DMF was evaporated. The residue was dissolved in EtOAc and purified by flash chromatography using EtOAc as eluant. ¹H NMR and MS data were
 5 consistent with the product.

Preparation of Intermediate V: 4-Cyanoisoquinoline



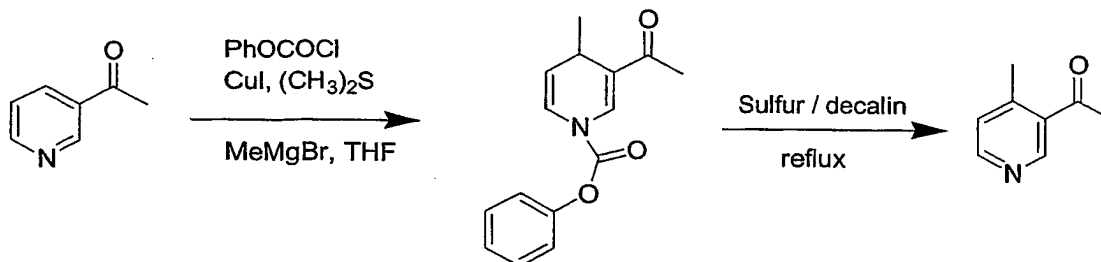
- 10 Into a 250 mL round-bottomed flask were placed 4-bromoisoquinoline (50.0 mmol, 10.4 g), CuCN (100.0 mmol, 9.0 g) and DMF (150 mL) under Ar. The solution was heated at 140 °C for 12 h. The reaction mixture was filtered over celite and the filtrate was concentrated. The residue was partitioned between CH₂Cl₂ (3 x 100 mL) and H₂O (100 mL), and then the organic layer was dried (Na₂SO₄). Concentration and purification of the crude product by
 15 column chromatography using 80:20 hexanes-EtOAc afforded 4-cyanoisoquinoline (45%).

Preparation of Intermediate W: Isoquinoline-4-thiocarboxamide



- 20 Isoquinoline-4-thiocarboxamide was prepared according to General Method B:
 TLC R_f 0.60 (EtOAc); ¹H NMR (DMSO-*d*₆) δ 10.4 (s, 1H), 9.9 (s, 1H), 8.6 (s, 1H), 9.3 (s, 1H), 8.4 (s, 1H), 8.2 (d, 1H), 7.8 (dd, 1H), 7.6 (dd, 1H); LCMS 189.1 (M+H⁺), t_R 1.08 min.

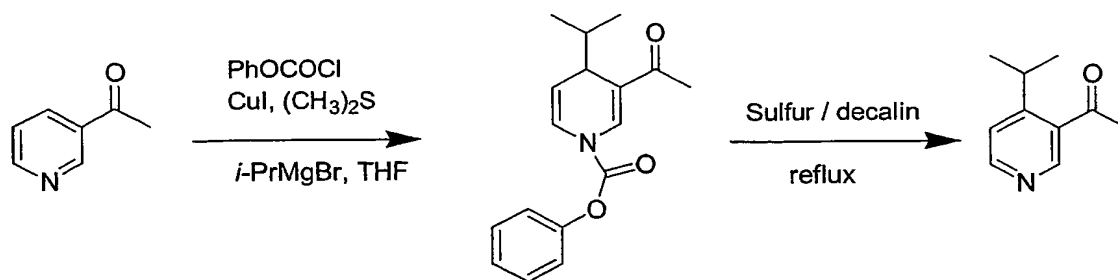
Preparation of Intermediate X: 4-Methyl-3-acetylpyridine



Step 1. A solution of 3-acetylpyridine (100 g, 0.82 mol), dimethyl sulfide (400 mL, 5.4 mol) and copper (I) iodide (7.94 g, 0.041 mol) in anhydrous THF (2 L) was stirred at rt under Ar. Phenyl chloroformate (0.4 mL, 0.82 mol) was then added, producing a dark brown precipitate. After 30 min, the mixture was cooled below -21°C and methyl magnesium bromide (1.4 M in 3:1 toluene-THF, 586 mL, 0.82 mol) was added over 50 min, keeping the reaction temperature below -15°C . The color lightened as the mixture became a solution; a lime green precipitate formed near the end of the addition, but redissolved upon completion. The mixture was stirred and allowed to warm slowly; after 2 h it had warmed to 8.8°C . Saturated aqueous ammonium chloride solution (500 mL) was added. After stirring for 10 min, the mixture was poured into a separatory funnel containing water (500 mL). The organic phase was separated, washed with brine (500 mL), dried (Na_2SO_4), filtered and then concentrated *in vacuo*. The residue was purified by silica gel chromatography using a hexane-EtOAc gradient to afford 134.3 g (63.7%) of the intermediate dihydropyridine.

Step 2. A solution of the intermediate dihydropyridine (134.3 g, 0.52 mol) in dichloromethane (100 mL) was added to a stirred suspension of sulfur (16.67 g, 0.52 mol) in decalin and slowly heated to reflux under an Ar sweep. After refluxing 1 h, the reaction mixture was allowed to cool to rt, then filtered through a pad of silica gel. After eluting the decalin with hexane, elution with a hexane-diethyl ether gradient afforded 49.4 g (70.3%) of 4-methyl-3-acetylpyridine as a reddish-brown oil: TLC R_f 0.19 (diethyl ether); TLC R_f 0.14 (1:1 hexane/EtOAc); ^1H NMR (CD_2Cl_2) δ 8.9 (s, 1H), 8.5 (d, 1H), 7.2 (dd, 1H), 2.6 (s, 3H); GCMS m/z 135 (M^+).

Preparation of Intermediate Y: 4-(2-Propyl)-3-acetylpyridine

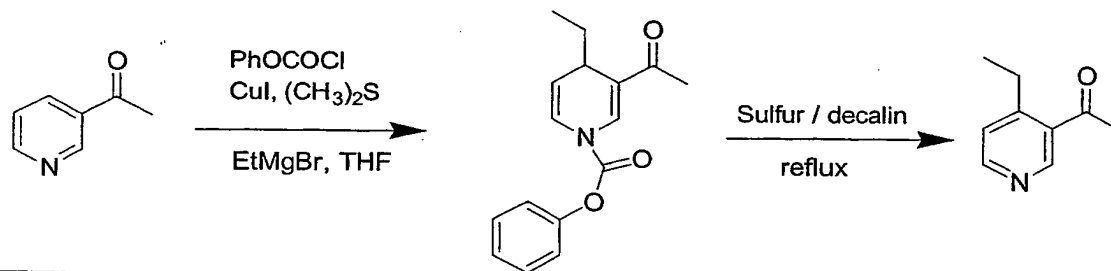


Step 1. To a mixture of CuI (78.5g, 0.412 mol), dimethyl sulphide (203 mL, 2.76 mol) and 3-acetyl pyridine (50.0g, 0.412 mol) in anhydrous THF (1100 mL) at rt was added phenyl

chloroformate (55.2 mL, 0.44 mol) and the mixture was stirred for 40-50 min. To this suspension at -25 to -20 °C was added isopropyl magnesium chloride (220 mL, 0.44 mol, 2.0 M solution in THF) over 30-40 min. The mixture was stirred at this temperature for 30 min, then warmed slowly to rt over 1.0-1.5 h. The reaction mixture was quenched with 20% NH_4Cl (350 mL), followed by extraction of the aqueous layer with EtOAc (700 mL). The organic layer was washed with 20% NH_4Cl (350 mL), then brine (250 mL), and dried over anhydrous Na_2SO_4 . Silica gel chromatography using a 3-10% EtOAc-hexane gradient yielded 43.5 g of crude 3-acetyl-4-isopropyl-1-phenoxyacetyl-1,4-dihydropyridine.

Step 2. A mixture of the crude dihydropyridine (43.5 g, 0.153 mol) and sulphur (4.9 g, 0.153 mol) were heated at reflux in decalin (175 mL) for a period of 3 h, then cooled to rt. Purification by silica gel chromatography, eluting first with hexanes, then with a 5-30% EtOAc-hexane gradient, gave 19.3 g (78%) of the title compound: TLC R_f 0.19 (25% EtOAc/hexane); GCMS (EI) t_R = 6.2 min; 163 (M^+); ^1H NMR (CDCl_3) δ 8.76 (s, 1H), 8.57 (d, 1H), 7.30 (d, 1H), 3.55 (m, 1H), 2.60 (s, 3H), 1.22 (d, 6H).

Preparation of Intermediate Z: 4-Ethyl-3-acetylpyridine

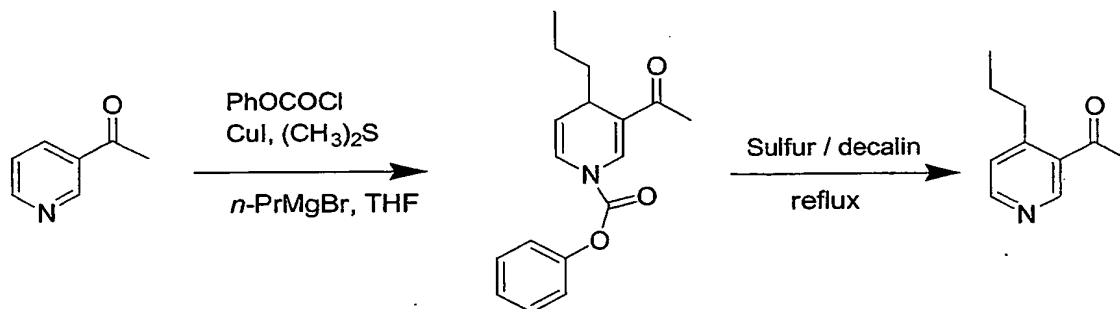


Step 1. 3-Acetylpyridine (5.0 g, 0.0413 mol), copper iodide (7.86 g, 0.0413 mol) and dimethyl sulfide (20.0 mL, 0.272 mol) were dissolved in THF (100 mL, anhydrous). This was stirred at rt for 15 min. To the reaction was added dropwise phenyl chloroformate (5.5 mL, 0.0441 mol) over 10 min. This reaction was then stirred under Ar for 1 h. The reaction was cooled to -25 °C and ethylmagnesium bromide (1M in THF, 44.1 mL, 0.0441 mol) was added dropwise over 40 min. The reaction was stirred at -25 °C for 30 min, then warmed to rt and quenched with 20% NH_4Cl (35 mL). The mixture was extracted with EtOAc, washed with 20% NH_4Cl , brine, and then dried over sodium sulfate. Regioisomers were produced in a 2:1 ratio (desired: undesired). The organic was concentrated to dryness and the crude oil

was purified by column chromatography (mobile phase 5% EtOAc/hexane). Phenyl 3-acetyl-4-ethyl-1(4H) pyridine carboxylate was obtained as an orange oil in 40.6 % yield, (4.55 g).

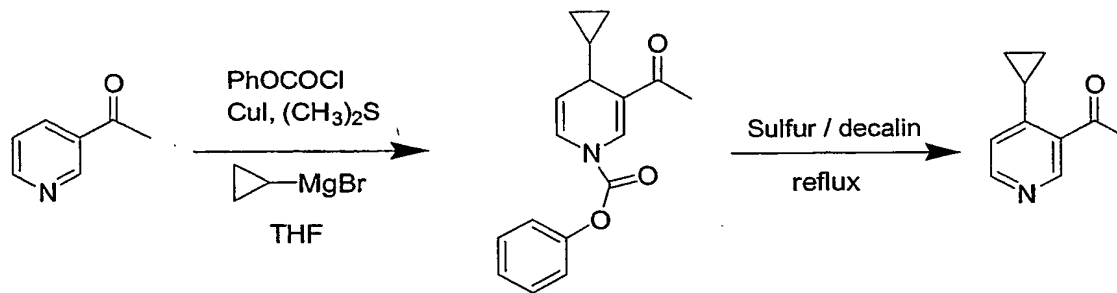
Step 2. Phenyl 3-acetyl-4-ethyl-1(4H)-pyridinecarboxylate (3.26 g, 0.0120 mol) and sulfur (0.385 g, 0.0120 mol) were dissolved into decalin (15 mL). The reaction mixture was heated to reflux for 17 h under Ar, then poured onto a silica gel column and washed with copious amounts of hexane. The product was then eluted with a gradient mobile phase (5% EtOAc/hexane to 30% EtOAc/hexane). The product containing fractions were concentrated to dryness to give an orange oil, 1.16 g (64.8%): R_f 0.12 (20% EtOAc/hexane).

Preparation of Intermediate AA: 4-(1-Propyl)-3-acetylpyridine



4-(1-Propyl)-3-acetylpyridine was prepared according to the method used to prepare 4-ethyl-3-acetylpyridine: LCMS t_R = 0.82 min; 164 ($\text{M}+\text{H}^+$); ^1H NMR (CDCl_3) δ 8.86 (s, 1H), 8.56 (d, J = 5 Hz, 1H), 7.20 (d, J = 5 Hz, 1H), 2.85 (t, J = 8 Hz, 2H), 2.63 (s, 3H), 1.61 (m, 2H), 0.97 t, J = 7 Hz, 3H).

Preparation of Intermediate AB: 4-Cyclopropyl-3-acetylpyridine



Step 1. Cyclopropyl bromide (50.0 g, 413 mmol) was dissolved in 500 mL of anhydrous THF. Dry magnesium (10.0 g, 411 mmol) was charged to a round-bottomed flask containing

a catalytic amount of iodine. 20% of the solution of the cyclopropyl bromide solution was then charged into the flask. After observing bubble formation, the remaining cyclopropyl bromide solution was added over 15 min, thereby causing the reaction mixture to reflux.

After 30 min, a 5.0 mL aliquot of the reaction mixture was taken to determine the concentration of the Grignard reagent. This analysis was performed according to the following procedure: 2 mg of 1,10 phenanthroline was added to a 50 mL flask with 10 mL of benzene; the 5.0 mL aliquot was then added; and the resulting mixture was titrated to the reddish-purple endpoint with 2.4 mL of 1.0 M butan-2-ol in p-xylene. Concentration was thus 0.48 M, which implied a 58% conversion to the desired Grignard reagent.

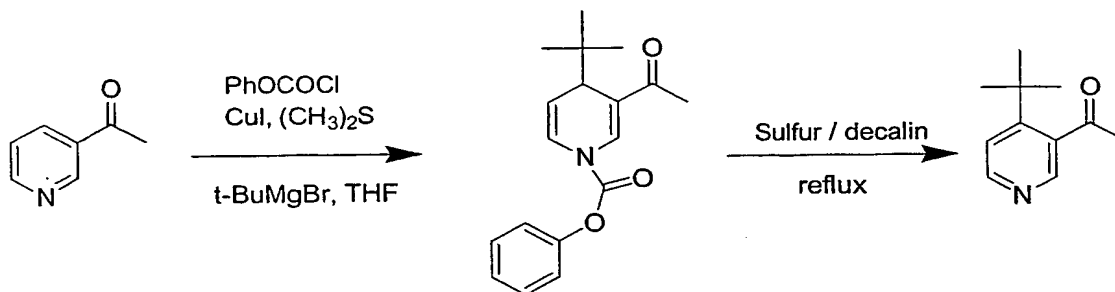
Step 2. 780 mg of CuI (4.10 mmol) was added to a round-bottomed flask under inert (Ar) conditions. A suspension was then formed by the addition of 100 mL of THF. 40 mL of dimethyl sulfide was added, yielding a clear yellow solution. 3-Acetylpyridine (10.0 g, 82.7 mmol) was then dissolved in 70 mL of THF and added to the yellow solution. Finally, 13.6 g (86.8 mmol) of phenyl chloroformate was dissolved in 50 mL of THF and the resulting solution was added slowly, resulting in the formation of a precipitate. The mixture was then cooled to -20 °C by packing the flask in dry ice. 172 mL (82.6 mmol) of the Grignard solution from above was then added dropwise over 20 min while maintaining the temperature below -5 °C. The reaction mixture was allowed to warm to rt and then quenched with 400 mL of 20% aqueous ammonium chloride. Ethyl acetate (200 mL) was added. The organic layer was collected and the aqueous layer was washed with 400 mL of ethyl acetate. The organic layers were combined, washed with brine, and then concentrated *in vacuo*. The residue was dissolved in dichloromethane and chromatographed on silica gel

using a Biotage Flash 75L column, first eluting with 2 L of 10% EtOAc-hexane, and then with 4 L of 15% EtOAc-hexane. The fractions containing the desired compound were combined and concentrated *in vacuo*, providing 12.2 g of an oil: ¹H NMR (CDCl₃) δ 7.98 (s, 1H, broad) 7.44 (t, 2H), 7.31 (t, 1H), 7.21 (d, 2H), 6.99 (s, 1H, broad), 5.20 (s, 1H, broad), 3.23 (t, 1H, broad), 2.40 (s, 3H), 0.91 (m, 1H), 0.53-0.33 (m, 3H), 0.20 (m, 1H); LCMS (ES) *m/z* 284.0 (M+H⁺).

Step 3. 12.2 g (43.0 mmol) of the dihydropyridine was transferred into a round-bottomed flask containing 143 mL of decahydronaphthalene. Sulfur (1.38 g, 43.0 mmol) was added and the flask was heated in an oil bath at 180 °C. Over 4 h, an additional 1.38 g of sulfur was added. The heat was then turned off and the reaction was diluted with 500 mL of MTBE. The organic layer was extracted twice with 250 mL portions of 1.0 N HCl. 500 mL

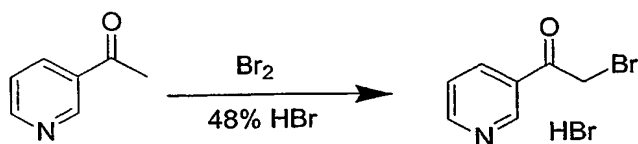
of dichloromethane was added to the aqueous layer, which was then made basic with 1.0 N NaOH. The organic layer was then washed with 250 mL of brine, dried with sodium sulfate, filtered, and concentrated to obtain 2.13 g of an oil. The acidic aqueous layers were extracted again with 500 mL of dichloromethane. The organic layer was dried with sodium sulfate, filtered into the oil obtained from above, and concentrated *in vacuo* to obtain a total of 3.63 g, (27% from 3-acetylpyridine): ^1H NMR (CDCl_3) δ 8.83 (s, 1H), 8.54 (d, 1H), 6.93 (d, 1H), 2.71 (m, 1H), 2.71 (s, 3H), 1.28 (d, 2H), 0.92 (d, 2H); LCMS (ES) m/z 162.1 ($\text{M}+\text{H}^+$); GCMS (CI) m/z 162 ($\text{M}+\text{H}^+$).

10 Preparation of Intermediate AC: 4-(*tert*-Butyl)-3-acetylpyridine



4-(*tert*-Butyl)-3-acetylpyridine was prepared according to the method used to prepare 4-ethyl-3-acetylpyridine to first give the intermediate phenyl 3-acetyl-4-*tert*-butyl-1(4H)-pyridinecarboxylate [HPLC t_R = 3.32 min; TLC R_f = 0.51 (5% EtOAc/hexane); ^1H NMR (CD_2Cl_2) δ 0.82 (s, 9H), 2.38 (s, 3H), 3.44 (d, 1H), 5.36-5.32 (m, 1H), 6.82 (d, 1H) 7.48-7.19 (m, 5H), 8.02 (s, 1H); LCMS (ES) m/z 300.3 ($\text{M}+\text{H}^+$)], which was then aromatized with sulfur to give the desired product 4-(*tert*-butyl)-3-acetylpyridine: HPLC t_R = 0.28; TLC R_f = 0.31 (EtOAc); LCMS (ES) m/z 177.92 ($\text{M}+\text{H}^+$).

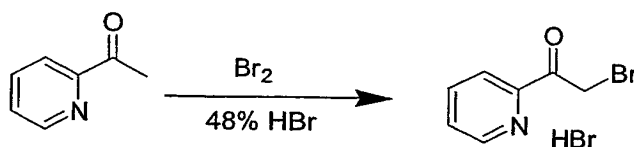
20 Preparation of Intermediate AD: 3-(2-Bromoacetyl)pyridine Hydrobromide



3-Acetylpyridine (4 g, 3.6 mL, 33 mmol) was added via syringe to a 3 necked round-bottomed flask that was equipped with a condenser, pressure equalizing dropping funnel and Ar inlet. 48% aqueous HBr (5.5mL) was added and the solution was placed in a 70 °C oil

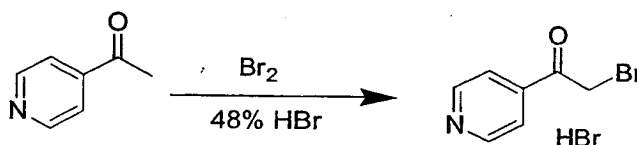
bath. Bromine (5.3 g, 1.7 mL) was added to the dropping funnel. The bromine was then diluted with 48% aqueous HBr (1 mL) and then the bromine solution was added dropwise into the reaction over 30 min. TLC taken after 2 h revealed that the reaction was completed. The reaction mixture was cooled to rt, during which time crystals precipitated out of the reaction solution. The crystals were filtered and rinsed with 24% aqueous HBr. The crude yield was 7.19 g (77%). The material was recrystallized from 24% aqueous HBr, providing 5.18 g (56%) of the title compound.

Preparation of Intermediate AE: 2-(2-Bromoacetyl)pyridine Hydrobromide



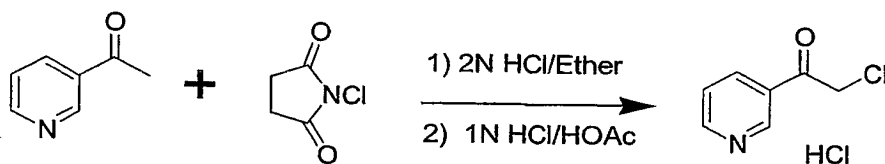
2-(2-Bromoacetyl)pyridine hydrobromide was prepared from 2-acetylpyridine according to the method used for 3-(2-bromoacetyl)pyridine hydrobromide, 23% yield.

Preparation of Intermediate AF: 4-(2-Bromoacetyl)pyridine Hydrobromide



4-(2-Bromoacetyl)pyridine hydrobromide was prepared from 4-acetylpyridine according to the method used for 3-(2-bromoacetyl)pyridine hydrobromide, 44% yield.

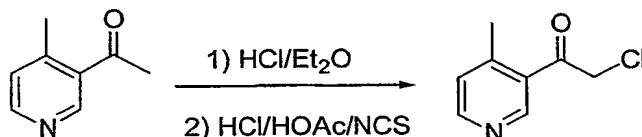
Preparation of Intermediate AG: 3-(2-Chloroacetyl)pyridine Hydrochloride



3-Acetylpyridine (5 g, 4.3 mL, 41.3 mmol) was dissolved in ether and the solution was cooled to 0 °C under Ar. A solution of 2N HCl/ether (1.2 eq, 25 mL) was added, and a white solid precipitated. The solid was rinsed with ether and dried, yielding 5.98 (92%) of the HCl

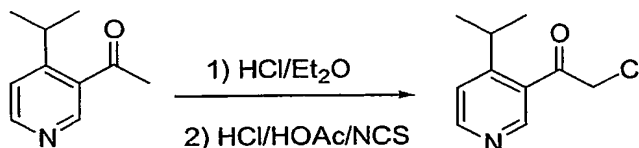
salt. The 3-acetyl pyridinium hydrochloride was then dissolved in 1 eq of 1N HCl. An equivalent of N-chlorosuccinimide was added and the reaction was refluxed overnight. Ether was added to the reaction mixture; a solid precipitated. The solid was washed with ether and dried under vacuum, providing 6.52 g (83%) of the title compound. The product
 5 was used without further purification.

Preparation of Intermediate AH: 4-Methyl-3-(2-chloroacetyl)pyridine



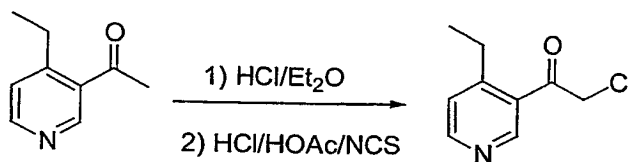
- 10 Into a 500 mL round-bottomed flask was placed 4-methyl-3-acetylpyridine (10.0 g, 74.1 mmol) in 90 mL of Et₂O. To this solution was added 88.9 mL of 1M HCl in Et₂O (1.2 eq, 88.9 mmol) and the solution allowed to stir for 1 h at rt, at which point, the precipitate was filtered and washed with Et₂O. The solid was then dried *in vacuo* at 60 °C. The HCl salt of 4-methyl-3-acetylpyridine (12.0 g, 70.0 mmol) was then dissolved in 70.0 mL of 1M HCl in
 15 acetic acid. Then 9.34 g (1 eq, 70.0 mmol) of N-chlorosuccinimide (NCS) was added, and the reaction allowed to stir under Ar at rt overnight. At this point, 300 mL of Et₂O was added, resulting in an off-white precipitate. This was allowed to stir for 1 h, then filtered and rinsed with Et₂O to provide 11.9 g (83%) of 4-methyl-3-(2-chloroacetyl)pyridine:
 GCMS *t_R* = 6.60 min, 169 (M⁺); ¹H NMR (DMSO-*d*₆) δ 2.51 (s, 3H), 5.15 (s, 2H), 7.68 (d,
 20 1H), 8.68 (d, 1H), 9.06 (s, 1H).

Preparation of Intermediate AI: 4-(2-Propyl)-3-(2-chloroacetyl)pyridine



25

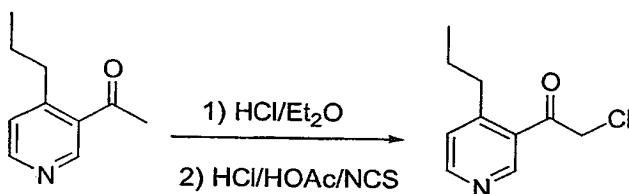
4-(2-Propyl)-3-(2-chloroacetyl)pyridine was prepared from 4-(2-propyl)-3-acetylpyridine according to the method used to prepare 4-methyl-3-(2-chloroacetyl)pyridine. MS and NMR data were consistent with the structure and the product was used without further purification.

Preparation of Intermediate AJ: 4-Ethyl-3-(2-chloroacetyl)pyridine

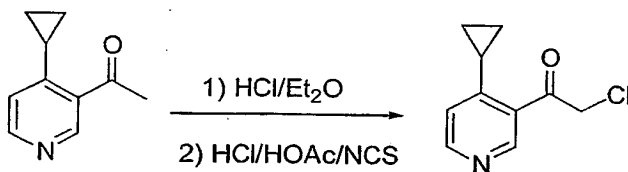
- 5 4-(2-Ethyl)-3-(2-chloroacetyl)pyridine was prepared from 4-(2-ethyl)-3-acetylpyridine according to the method used to prepare 4-methyl-3-(2-chloroacetyl)pyridine. MS and NMR data were consistent with the structure and the product was used without further purification.

Preparation of Intermediate AK: 4-(1-Propyl)-3-(2-chloroacetyl)pyridine

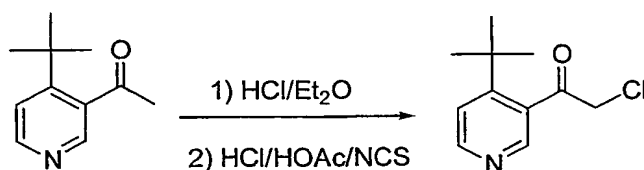
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- 15 4-(1-Propyl)-3-(2-chloroacetyl)pyridine was prepared from 4-(1-propyl)-3-acetylpyridine according to the method used to prepare 4-methyl-3-(2-chloroacetyl)pyridine. MS and NMR data were consistent with the structure and the product was used without further purification.

Preparation of Intermediate AL: 4-Cyclopropyl-3-(2-chloroacetyl)pyridine

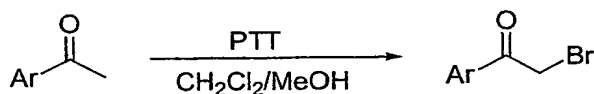
- 20 4-(Cyclopropyl)-3-(2-chloroacetyl)pyridine was prepared from 4-(cyclopropyl)-3-acetylpyridine according to the method used to prepare 4-methyl-3-(2-chloroacetyl)pyridine. MS and NMR data were consistent with the structure and the product was used without further purification.

Preparation of Intermediate AM: 4-(*tert*-Butyl)-3-(2-chloroacetyl)pyridine

5 4-(*tert*-Butyl)-3-(2-chloroacetyl)pyridine was prepared from 4-(*tert*-butyl)-3-acetylpyridine according to the method used to prepare 4-methyl-3-(2-chloroacetyl)pyridine. MS and NMR data were consistent with the structure and the product was used without further purification.

General Method C: Synthesis of Non-commercially Available α -Bromo Aryl Ketones

10



15 To a solution of aryl ketone (12 mmol) in dichloromethane (20 mL) and methanol (2 mL) was added a solution of phenyltrimethylammonium tribromide (PTT) (4.68 g, 12 mmol) in dichloromethane (20 mL) and methanol (2 mL) dropwise. The red-colored reaction was stirred 4 h at rt after which time the color had changed to light-yellow. The solvents were evaporated *in vacuo* and the residue was partitioned between EtOAc (75 mL) and H₂O (50 mL). The separated organic phase was washed with H₂O (50 mL), brine (50 mL), and then dried over Na₂SO₄. The solvent was evaporated *in vacuo*, giving the desired alpha bromo
 20 ketone intermediate, which was used in the next step without purification. NMR and MS spectral data were consistent with the structure.

The following alpha bromo aryl ketones were prepared according to General Method C:

25 Intermediate AN: 2-(Bromoacetyl)-5-chlorothiophene was synthesized from 2-acetyl-5-chlorothiophene (87%).

Intermediate AO: 2-(Bromoacetyl)-5-methylfuran was synthesized from 2-acetyl-5-methylfuran (93%).

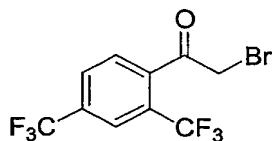
30 Intermediate AP: 2-Bromo-4'-chloropropiophenone was synthesized from 4'-chloropropiophenone (86%).

Intermediate AQ: 2-(Bromoacetyl)-4-phenoxybenzene was synthesized from 4-phenoxyacetophenone (62%).

Intermediate AR: 2-Bromo-4-(4-chlorophenyl)acetophenone was synthesized from 4-(4-chlorophenyl)acetophenone (69%).

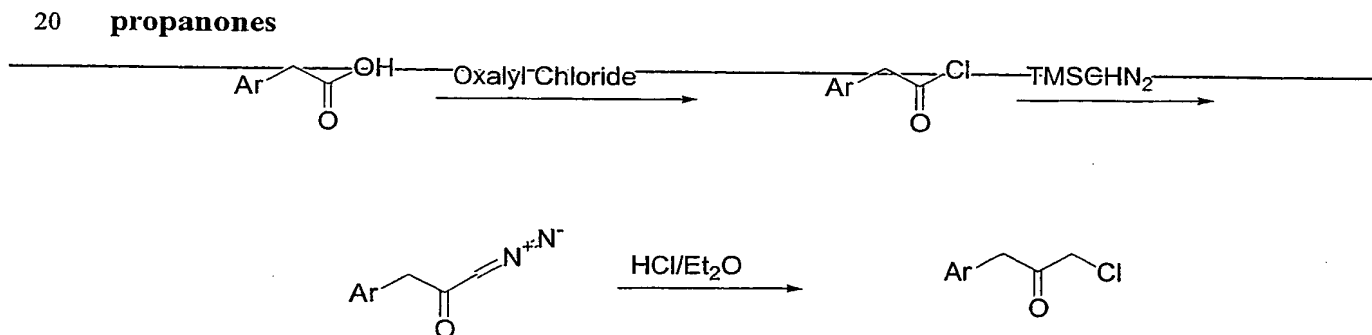
- 5 Intermediate AS: 2-(2-Bromoacetyl)-5-methylfuran was synthesized from 2-acetyl-5-methylfuran (51%).

Preparation of Intermediate AT: 2-Bromo-2', 4'-di(trifluoromethyl)acetophenone



- 10 A solution of 2,4-di(trifluoromethyl)acetophenone (5.0 g, 19.52 mmol) in anhydrous tetrahydrofuran under Ar was treated with phenyltrimethylammonium tribromide (7.34 g, 19.52 mmol, 1.0 eq) at 0 °C. The reaction mixture was stirred at ambient temperature for 17 h and then concentrated. The crude material was redissolved in EtOAc (250 mL). The organic layer was washed with water (2 x 250 mL) and brine (1 x 150 mL), dried (MgSO₄),
15 filtered, and then evaporated *in vacuo*. Crystallization from hexane at 0 °C afforded a white crystalline solid. The product was filtered and rinsed well (3 x) with hexane to give 3.78 g (57.8%) of a white solid: GCMS *m/z* 333 (*M*⁺), 335 (*M*+2⁺).

General Method D: Synthesis of Non Commercially Available 3-Aryl-1-chloro-2-propanones



- A solution of the arylacetic acid (13 mmol) in CH₂Cl₂ (30 mL) was treated with 2.0 M oxalyl chloride in CH₂Cl₂ (14 mmol) via syringe. This was treated with 2 drops of DMF, which caused a vigorous gas evolution. The reaction was stirred 3 h, then the CH₂Cl₂ was
25 evaporated *in vacuo*. The residue was dissolved in THF (15 mL) and acetonitrile (15 mL),

cooled to 0 °C, and then treated dropwise with 2.0 M (trimethylsilyl)diazomethane in hexanes (27 mmol). The mixture was stirred while warming to rt overnight. The solvents were removed *in vacuo*. The residue was dissolved in diethyl ether (30 mL), cooled to 0 °C, and then treated dropwise with 2.0 M HCl in ether (27 mmol), which caused a vigorous gas evolution. The reaction was stirred 30 min, the solvent removed *in vacuo*, and the residue purified via flash chromatography (0-1% EtOAc/hexane), providing the desired 3-aryl-1-chloropropanone intermediate. The NMR and MS spectral data were consistent with the structure. In some cases, the necessary intermediate acid chloride was commercially available, which made its preparation from the arylacetic acid unnecessary.

The following intermediates were prepared using Method D:

Intermediate AU: 1-(4-Methylphenyl)-3-chloro-2-propanone was synthesized from 1-methylphenyl acetic acid (90%).

Intermediate AV: 1-(4-Chlorophenyl)-3-chloro-2-propanone was synthesized synthesized from 4-chlorophenylacetyl chloride (82%).

Intermediate AW: 1-(3-Chlorophenyl)-3-chloro-2-propanone was synthesized synthesized from 3-chlorophenylacetic acid (70%).

Intermediate AX: 1-(3-Methylphenyl)-3-chloro-2-propanone was synthesized synthesized from 3-methylphenylacetic acid (58%).

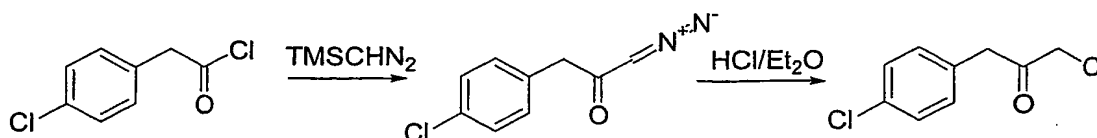
Intermediate AY: 1-(4-Fluorophenyl)-3-chloro-2-propanone was synthesized synthesized from 4-fluorophenylacetic acid (79%).

Intermediate AZ: 1-(3,4-Dichlorophenyl)-3-chloro-2-propanone was synthesized synthesized-from-3,4-dichlorophenylacetic-acid-(45%)

Intermediate BA: 1-(3-Nitrophenyl)-3-chloro-2-propanone was synthesized from 3-nitrophenylacetic acid (62%).

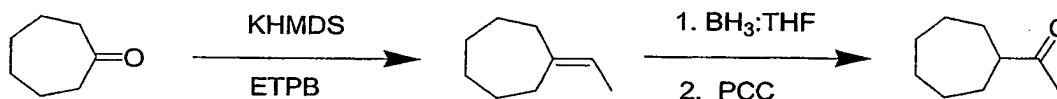
Intermediate BB: 1-(4-Bromophenyl)-3-chloro-2-propanone was synthesized synthesized from 4-bromophenylacetic acid.

Preparation of Intermediate BC: 1-(4-Chlorophenyl)-3-chloro-2-propanone



A solution of trimethylsilyldiazomethane in hexane (2.0 M, 23 mL, 46.1 mmol) was added dropwise, over a 9 min period, to a solution of 4-chlorophenylacetyl chloride (8.89 g, 46.1 mmol) in a mixture of anhydrous acetonitrile (135 mL) and anhydrous THF (135 mL) that was held at 0 °C under Ar. After stirring overnight at rt, concentration *in vacuo* gave a pale yellow oil, which was purified by silica gel chromatography (hexane-dichloromethane solvent gradient) to afford 8.44 g (94.2%) of pale yellow solid intermediate. A stirred solution of the diazo intermediate (8.4 g, 43.4 mmol) in diethyl ether (240 mL) was treated dropwise with hydrogen chloride (2M) in ether over a 10 min period. Gentle bubbling was observed, as well as a mild rise in the reaction temperature. After stirring overnight at rt, TLC showed no remaining intermediate. The mixture was concentrated *in vacuo* to afford 4.73 g (53.7%) of the title compound as tan, opaque crystals, mp 40.5-45.5°C: ¹H NMR (CDCl₃) δ 7.3 (d, 2H), 7.2 (d, 2H), 4.1, (s, 2H), 3.9 (s, 2H); GCMS *m/z* 202 (M⁺).

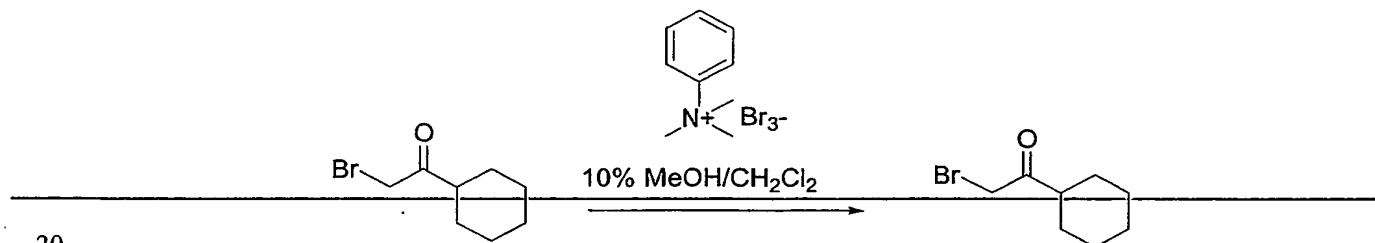
General Method E: Synthesis of Cycloalkyl and Bicycloalkyl Methyl Ketones as Exemplified by the Preparation of Acetylcycloheptane (Intermediate BD).



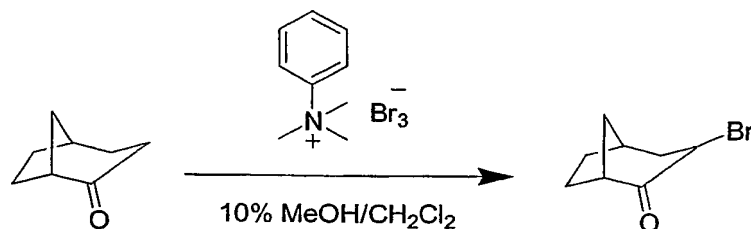
Step 1. To a stirring suspension of ethyltriphenylphosphonium bromide (ETPB) (25.0 g, 67.34 mmol) in anhydrous THF (80 mL) at 0 °C was added KHMDS (135 mL of a 0.5 M/toluene solution, 67.34 mmol) dropwise over 30 min. The red suspension was stirred 15 min at 0 °, then a solution of cycloheptanone (6.87 g, 61.22 mmol) in THF (10 mL) was added over 30 min. The orange suspension was stirred to rt over 3 h with the ice bath removed then at rt for 16 h. The reaction was quenched with water (200 mL) and extracted with hexane (2 x 400 mL). The organic was dried (Na₂SO₄) and concentrated *in vacuo* to give an oil with solids (triphenylphosphonium oxide). The oil was triturated in hexane and filtered to remove the solid repeatedly until a yellow oil remains. This was purified by a silica gel plug (hexane) to give the product as a clear oil in 22% yield (1.68 g, 13.55 mmol): ¹H NMR (CDCl₃) δ 4.96 (1H, m), 1.95 (4H, m), 1.18-1.37 (11H, m).

Step 2. To a solution of cyclohexylethylidene (1.60 g, 12.88 mmol) in dry THF (75 mL) at 0 °C was added BH₃:THF complex (9.02 mL of a 1.5 M THF/ether solution, 13.52 mmol) over 5 min. The solution was stirred at 0 °C for 1 h then quenched by slow dropwise addition of water (H₂ evolution). The quenched reaction was further diluted with water (100 mL) and extracted with Et₂O (2 x 250 mL). The organic was dried (MgSO₄) and concentrated and the residue dried under P₂O₅ *in vacuo*. The crude intermediate was dissolved in CH₂Cl₂ (100 mL) and PCC added (5.55 g, 25.76 mmol) followed by 4 Å molecular sieves activated powder (5.55 g). This was refluxed vigorously for 3 h. More CH₂Cl₂ (50 mL), PCC (14.0 g, 64.95 mmol), and 4 Å molecular sieves powder (11 g) were added and the reaction refluxed for 16 h. The reaction was diluted with more water (200 mL) and extracted with CH₂Cl₂ (3 x 300 mL). The organic layer was dried (Na₂SO₄) and filtered directly through a plug of silica gel to give the product as a clear oil in 83% yield (1.66 g, 10.70 mmol): TLC R_f 0.18 (5% EtOAc/hexane); GCMS (EI) *m/z* 140 (M)⁺, *t_R* = 5.30 min.

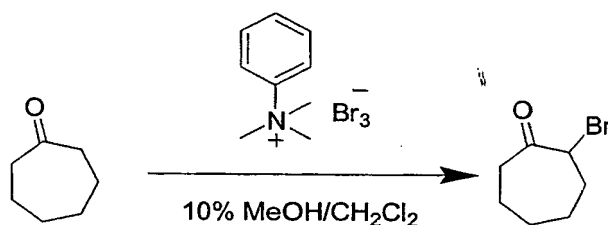
General Method F: Synthesis of 2-Bromomethyl Cycloalkyl Ketones and 2-Bromomethyl Bicycloalkyl Ketones as Exemplified by the Preparation of 2-Bromoacetylcyclohexane (Intermediate BE).



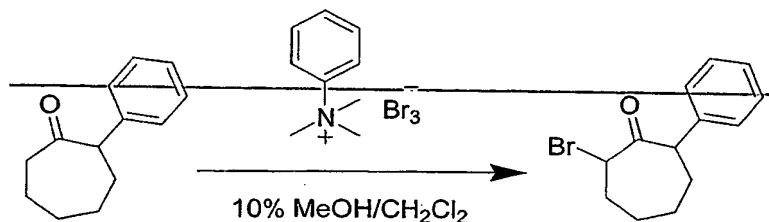
A solution of cyclohexylmethyl ketone (2.50 g, 19.8 mmol) in dry CH₂Cl₂ (20 mL) and MeOH (2 mL) was treated with a solution of phenyltrimethylammonium tribromide (7.45 g, 19.8 mmol) in dry CH₂Cl₂ (20 mL) and MeOH (2 mL) dropwise over 2 h at rt. The reaction was stirred an additional 2 h at rt, then the reaction was concentrated and redissolved in Et₂O (200 mL). This was washed with water (2 x 100 mL) and dried (Na₂SO₄). The crude product was purified by silica gel chromatography to give the product as a clear oil in 32% yield (1.29 g, 6.31 mmol): TLC R_f 0.35 (5% EtOAc/hexane); GCMS (CI) 205 *m/z* (M+H)⁺, *t_R* = 6.08 min.

Preparation of Intermediate BF: 3-Bromobicyclo[3.2.1]octan-2-one

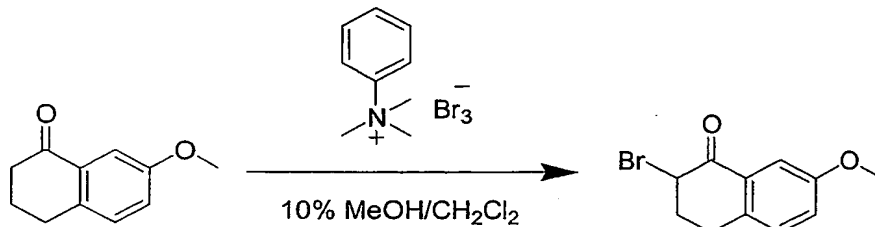
3-Bromobicyclo[3.2.1]octan-2-one was prepared according to General Method F from bicyclo[3.2.1]octanone: TLC R_f 0.30 (10% EtOAc/hexane); GCMS (EI) *m/z* 202 (M+H)⁺, t_R = 7.00 min.

Preparation of Intermediate BG: 2-Bromocycloheptanone

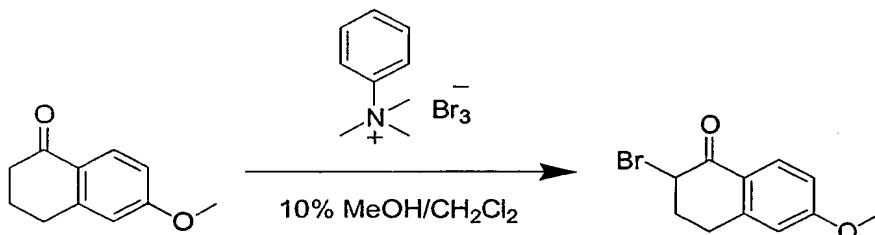
2-Bromocycloheptanone was prepared according to General Method F from cycloheptanone: TLC R_f 0.25 (100% hexane); GCMS (EI) *m/z* 190 (M)⁺, t_R = 5.91 min.

Preparation of Intermediate BH: 2-Bromo-7-phenylcycloheptanone

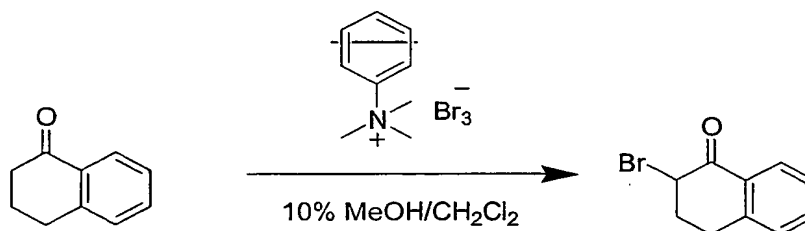
2-Bromo-7-phenylcycloheptanone was prepared according to General Method F from 2-phenylcycloheptanone: TLC R_f 0.33 (5% EtOAc hexane); GCMS (EI) 266 (M)⁺, t_R = 8.82 min.

Preparation of Intermediate BI: 2-Bromo-7-methoxy-1-tetralone

2-Bromo-7-methoxy-1-tetralone was prepared according to General Method F from 7-methoxy-1-tetralone: TLC R_f 0.55 (15% EtOAc/hexane); GCMS (EI) *m/z* 254/255 (M)⁺, t_R = 8.50 min.

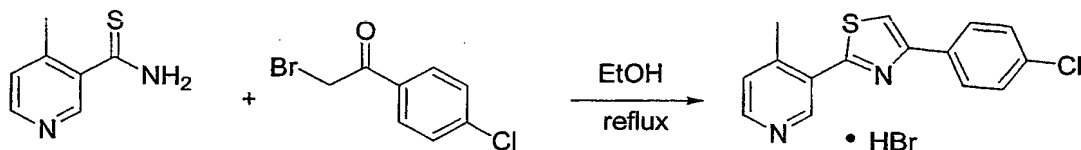
Preparation of Intermediate BJ: 2-Bromo-6-methoxy-1-tetralone

2-Bromo-6-methoxy-1-tetralone was prepared according to General Method F from 6-methoxy-1-tetralone: TLC R_f 0.20 (40% CH₂Cl₂/hexane); GCMS (EI) *m/z* 254/255 (M)⁺, t_R = 9.05 min.

Preparation of Intermediate BK: 2-Bromo-1-tetralone

2-Bromo-1-tetralone was prepared according to General Method F from α-tetralone: TLC R_f 0.50 (5% EtOAc/hexane); GCMS (EI) *m/z* 224/225 (M)⁺, t_R = 8.00 min.

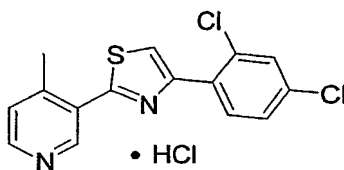
Example 1**Preparation of 2-(4-Methyl-3-pyridyl)-4-(4-chlorophenyl)thiazole Hydrobromide**



A mixture of 4-methylpyridine-3-thiocarboxamide (2.0 g, 13.1 mmol), 4-chlorophenyl bromide (3.12 g, 13.1 mmol) and absolute ethanol (100 mL) was refluxed overnight under an Ar atmosphere. After cooling in ice water, the solid was filtered, sequentially washed with ethanol and hexane, and then dried to afford 4.26 g (88.4%) of a pale yellow solid. A 1.0 g portion was recrystallized from distilled water to afford 0.37 g as pale yellow crystals, mp 279.5-286 °C: TLC R_f 0.45 (5% methanol/ dichloromethane); TLC R_f 0.41 (EtOAc); ¹H NMR (DMSO-*d*₆) δ 9.2 (s, 1H), 8.7 (d, 1H), 8.5 (s, 1H), 8.1 (dd, 2H), 7.9 (d, 1H), 7.5 (dd, 2H); 5.2 (broad exchangeable, 1H); 2.8 (s, 3H); LCMS 287 (M+H⁺), 289 (M+H+2⁺). Anal. Calcd for C₁₅H₁₁ClN₂S • HBr: C, 49.00; H, 3.29; N, 7.62; Br, 21.73; Cl, 9.64; S, 8.72. Found: C, 49.73; H, 3.24; N, 7.6; Br, 20.38; Cl, 9.84; S, 8.8.

Example 2

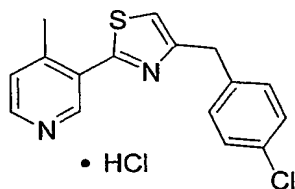
Preparation of 2-(4-Methyl-3-pyridyl)-4-(2,4-dichlorophenyl)thiazole Hydrochloride



2-(4-Methyl-3-pyridyl)-4-(2,4-dichlorophenyl)thiazole hydrochloride was prepared from 4-methylpyridine-3-thiocarboxamide and 2,2',4'-trichloroacetophenone according to the procedure used in Example 1 to afford 1.78 g (61.1%) of the title compound: TLC R_f 0.42 (5% methanol/dichloromethane); TLC R_f 0.43 (EtOAc); ¹H NMR (DMSO-*d*₆) δ 9.2 (s, 1H), 8.7 (d, 1H), 8.4 (s, 1H), 8.0 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.58 (d, 1H), 7.55 (d, 1H), 7.0 (broad exchangeable, 1H), 2.8 (s, 3H); LCMS 321 (M+H⁺); 323 (M+2+H⁺). Anal. Calcd for C₁₅H₁₀Cl₂N₂S • HCl: C, 50.37; H, 3.1%; N, 7.83; Cl, 29.74; S, 8.96. Found: C, 50.43; H, 3.1; N, 7.85; Cl, 29.5; S, 8.99.

Example 3

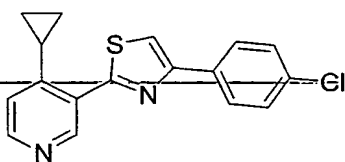
Preparation of 2-(4-Methyl-3-pyridyl)-4-(4-chlorophenylmethyl)thiazole Hydrochloride



2-(4-Methyl-3-pyridyl)-4-(4-chlorophenylmethyl)thiazole was prepared according from 4-methylpyridine-3-thiocarboxamide and 1-chloro-3-(4-chlorophenyl)-2-propanone according to the procedure used in Example 1 to yield, after chromatography, 1.88 g (47.7%). This material was dissolved in dichloromethane, filtered, and then the filtrate was stirred while hydrogen chloride (2M in diethyl ether) was added. After removal of solvent *in vacuo*, the solid was triturated with ether, filtered and washed to afford 1.60 g (36.9%) of 2-(4-methyl-3-pyridyl)-4-(4-chlorophenylmethyl)thiazole hydrochloride as a tan-brown solid, mp 165.5 – 170 °C: TLC R_f 0.12 (2% methanol in dichloromethane); TLC R_f 0.39 (EtOAc); ¹H NMR (DMSO-*d*₆) δ 9.1 (s, 1H), 8.7 (d, 1H), 7.9 (d, 1H), 7.7 (s, 1H), 7.3 (s, 4H), 4.2 (s, 2H), 2.7 (s, 3H); LCMS 301 (M+H⁺); 303 (M+H+2⁺). Anal. Calcd for C₁₆H₁₃ClN₂S •HCl: C, 56.98; H, 4.18; N, 8.31; Cl, 21.02; S, 9.51. Found: C, 56.86; H, 4.18; N, 8.02; Cl, 21.28; S, 9.11.

Example 4

Preparation of 2-(4-Cyclopropyl-3-pyridyl)-4-(4-chlorophenyl)thiazole.

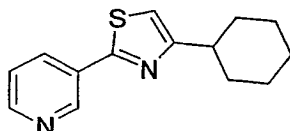


A solution of 4-cyclopropyl-3-pyridinecarbothioamide (1.53 g, 8.6 mmol), 4-chlorophenacyl bromide (2.25 g, 9.5 mmol) in absolute ethanol (30 mL) was heated to reflux for 16-18 h. The resulting precipitate was cooled in an ice bath for 2-2.5 h, filtered, and then washed with cold absolute ethanol (5 mL). The hydrochloride salt so obtained was converted to the free base with sodium bicarbonate, then extracted with dichloromethane and concentrated. Silica gel chromatography, using 5-20% EtOAc-hexane, yielded 1.5 g (56%) of the pure product: LCMS t_R 2.65 min, 313 (M+H⁺); ¹H NMR (CDCl₃) δ 8.95 (1H, s), 8.52 (1H, d), 7.92 (2H,

d), 7.64 (1H, s), 7.43 (2H, d), 6.94 (1H, d), 2.68 (1H, m), 1.23 (2H, m), 0.94 (2H, m). Anal. Calcd for $C_{17}H_{13}N_2ClS$: C, 65.27; H, 4.19; N, 8.96. Found: C, 65.02; H, 4.35; N, 8.85.

Example 5

5 General Method G, as Exemplified by the Preparation of 2-(3-Pyridyl)-4-(cyclohexyl)thiazole



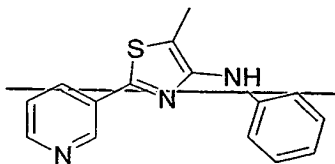
10

To a solution of thionicotinamide (202 mg, 1.46 mmol) in abs. ethanol (10 mL) was added 2-bromoacetyl cyclohexane (300 mg, 1.46 mmol) and the solution refluxed for 2.5 h. The reaction was concentrated *in vacuo*, and the residue suspended in CH_2Cl_2 . The crude product was free-based with triethylamine (0.24 mL), and purified by silica gel chromatography to give 256 mg (72%) of the title product in 72% yield as a clear oil: TLC R_f 0.24 (25% EtOAc/hexane); LCMS (ES) 245 (M+H)⁺, t_R = 2.46 min.

15

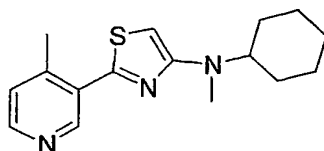
Example 6

20 General Procedure H, as Exemplified by the Preparation of 2-(3-pyridyl)-4-(phenylamino)-5-methylthiazole

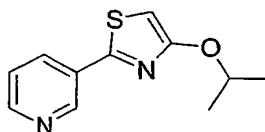


25

A homogenous mixture of thionicotinamide (1.00 g, 7.236 mmol) and 2-bromo-N-phenylpropionamide (1.65 g, 7.24 mmol) was melted at 110 °C for 20 h. The melt was suspended in CH_2Cl_2 (50 mL) and free-based with triethylamine (1.01 mL). The suspension was filtered to remove starting material and the filtrate purified by silica gel chromatography to give the product as light yellow crystals in 3% yield (53 mg, 0.20 mmol): TLC R_f 0.33 (50% EtOAc/hexane); LCMS (ES) 268 (M+H)⁺, t_R = 2.29 min.

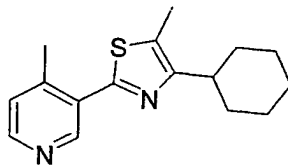
Example 7**Preparation of 2-(4-Methyl-3-pyridyl)-4-(N-methylcyclohexylamino)thiazole**

5 To a solution of 4-methyl thionicotinamide (602 mg, 3.95 mmol) in dry DMF (15 mL) at 100 °C was added 2-chloro-N-cyclohexyl-N-methylacetamide (600 mg, 3.16 mmol) dropwise as a solution in dry DMF (5 mL) over 10 min. The reaction was stirred for 1.5 h at 100 °C, then diluted with water (100 mL) and extracted with Et₂O (2 x 200 mL). The
10 organic layer was washed with water (50 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the product as an oil in 0.5% yield (4 mg, 0.014 mmol): TLC R_f 0.52 (50% EtOAc/hexane); LCMS (ES) 288 (M+H)⁺, t_R = 2.59 min.

Example 8**General Method I, as Exemplified by the Preparation of 2-(3-Pyridyl)-4-(isopropoxy)thiazole**

20 A suspension of thionicotinamide (977 mg, 7.07 mmol) and N-(bromoacetyl)-3,5-dichloroaniline (1.00 g, 3.53 mmol) in isopropanol (30 mL) was refluxed for 16 h. The solvent was then boiled off and the solid residue suspended in CH₂Cl₂ (20 mL). The crude suspension was free-based with triethylamine (0.985 mL), and filtered to remove the pure 4-
25 (3,5-dichlorophenyl)aminothiazole side-product. Purification by silica gel chromatography gave the product as a clear oil in 19% yield (146 mg, 0.663 mmol): TLC R_f 0.28 (25% EtOAc/hexane); LCMS (ES) 221 (M+H)⁺, t_R = 1.96 min.

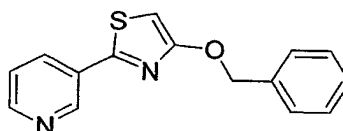
Example 9**General Method J, as Exemplified by the Preparation of 2-(4-Methyl-3-pyridyl)-4-(cyclohexyl)-5-methylthiazole**



To an LDA solution (0.581 mmol) in dry THF (5 mL) at -78°C was added 2-(4-methylpyridyl)-4-cyclohexylthiazole (100 mg, 0.387 mmol) as a solution in dry THF (5 mL) dropwise over 10 min. The red suspension was stirred for 30 min at -78°C , then iodomethane (549 mg, 3.87 mmol) was added. The reaction was warmed to rt over 1 h with the ice bath removed. The clear reaction was then concentrated *in vacuo* and the residue purified by silica gel chromatography to give the product as an amber oil in 91% yield (96 mg, 0.35 mmol): TLC R_f 0.63 (50% EtOAc/hexane); LCMS (ES) 273 ($\text{M}+\text{H}^+$), t_R = 2.65 min.

Example 10

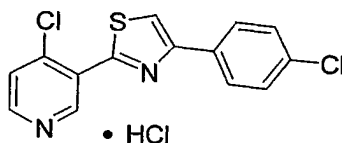
General Method K, as Exemplified by the Preparation of 2-(3-Pyridyl)-4-(benzyloxy)thiazole



Thionicotinamide (1.00 g, 7.236 mmol) was heated in neat benzyl bromoacetate (8.29 g, 36.2 mmol) at 90°C for 1 h. The reaction was diluted with CH_2Cl_2 (30 mL) and quenched with triethylamine (2.02 mL). This was purified by silica gel chromatography to give the product as an orange solid in 3% yield (51 mg): R_f 0.40 (50% EtOAc/hexane); LCMS (ES) 269 ($\text{M}+\text{H}^+$), t_R = 3.10 min.

Example 11

Preparation of 2-(4-Chloro-3-pyridyl)-4-(4-chlorophenyl)thiazole (Intermediate BF)

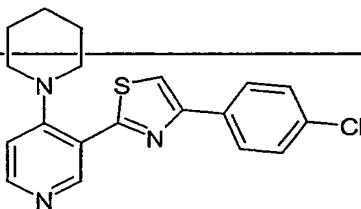


Step 1. A mixture of 4-methoxypyridine-5-thiocarboxamide (0.50 g, 3 mmol) and 2-bromo-4'-chloroacetophenone (0.69 g, 3 mmol) in ethanol (40 mL) was refluxed overnight, during which time a yellow precipitate formed. The reaction mixture was cooled and the solvent evaporated *in vacuo*. The residue was triturated in CH₂Cl₂, filtered, and then washed with CH₂Cl₂ (2x50 mL). The material was triturated a second time with 20% MeOH in CH₂Cl₂, filtered, and washed with CH₂Cl₂. Drying under vacuum gave 0.47 g (54%) of 2-(3-pyridin-4-one)-4-(4-chlorophenyl)thiazole as a tan solid.

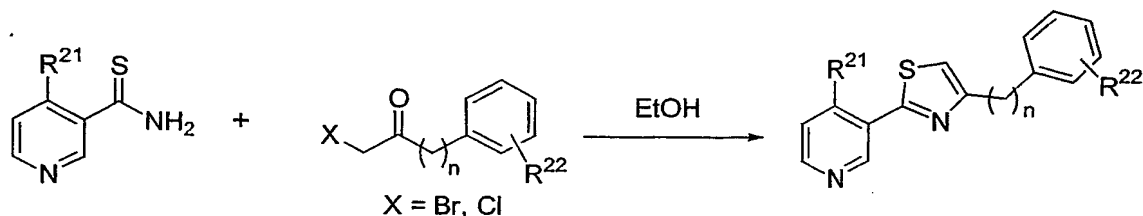
Step 2. A stirred mixture of 2-(3-pyridin-4-one)-4-(4-chlorophenyl)thiazole (4.06 g, 14.1 mmol) and phosphorus oxychloride (66 mL, 703 mmol) was heated under an Ar atmosphere and allowed to reflux for 16.5 h. After allowing the mixture to cool to rt, the solid was filtered and triturated on the funnel twice with dichloromethane. After drying, 4.6 g of the title compound was obtained as a pale yellow solid, mp 176.5-183.5 °C: TLC R_f 0.33 (2% methanol in dichloromethane); TLC R_f 0.45 (1:1 hexane-EtOAc); ¹H NMR (DMSO-*d*₆) δ 9.4 (s, 1H), 8.6 (d, 1H), 8.5 (s, 1H), 8.1 (d, 2H), 7.8 (d, 1H), 7.5 (d, 2H), 7.2 (broad exchangeable, 1H); LC MS 307 (M+H⁺), 309 (M+2+H⁺). Anal. Calcd for C₁₄H₈Cl₂N₂S: C, 48.93; H, 2.64; N, 8.15; Cl, 30.95; S, 9.33. Found: C, 48.75; H, 2.43; N, 7.73; Cl 31.44; S, 8.98.

Example 12

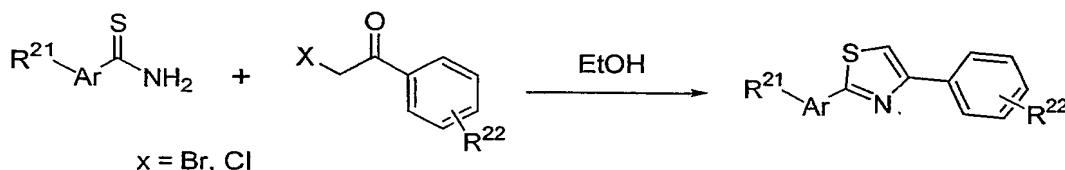
General Method L, as Exemplified by the Preparation of 3-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-(1-piperidinyl)pyridine.



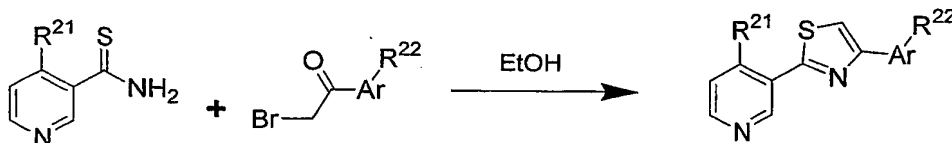
4-Chloro-3-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]pyridine (70.0 mg, 0.2 mmol) and piperidine (80.6 μL, 0.8 mmol) were dissolved in THF (4 mL). To this solution was added 1% v/v HCl (0.1 mL). The reaction was refluxed overnight. The mixture was concentrated under reduced pressure. The compound was purified by Gilson HPLC to yield 58.0 mg (81.5%) of a pale yellow oil.

General Method M: Synthesis of 2-(3-Pyridyl)Thiazoles

A mixture of the pyridine thiocarboxamide (1 mmol) and the alpha-bromo or
 5 alpha-chloro ketone (1 mmol) in ethanol (15 mL) was refluxed together overnight. The
 reaction was cooled and the solvent evaporated *in vacuo*. The residue was treated with
 triethylamine to liberate the free base of the product, and the residue was purified by flash
 chromatography (10 – 20% EtOAc/hexane) to provide the desired 2-(3-pyridyl)thiazole
 derivative. The yields ranged from 45 – 90%.

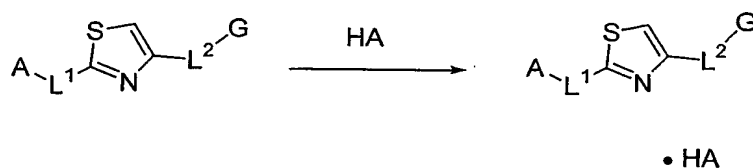
General Method N: Synthesis of 2-(3-Pyridyl)-Thiazoles and 2-(4-Isoquinoliny)-Thiazoles

In a 250 mL round-bottomed flask were placed the pyridine thiocarboxamides (18.0 mmol)
 15 and the requisite bromoketone (1.1 eq, 19.9 mmol) in 100 mL EtOH. The reaction mixture
 was heated at 70°C for 8 h under Ar and then concentrated. The residue was partitioned
 between CH₂Cl₂ (3 x 100 mL), H₂O (100 mL), and Et₃N (5 mL). The organic layer was
 dried over Na₂SO₄ and concentrated. Purification by chromatography using 80/20 hexanes-
 EtOAc afforded the target thiazole derivatives. The yield ranged from 50-85%.

General Method O: Synthesis of 2-(3-Pyridyl)-Thiazoles by Parallel Methods

An EPA vial was charged with 4-cyclopropyl-3-pyridinecarbothioamide (11.2 mmol) and the α -halo ketone (13.5 mmol, 1.20 eq). To this was added 15 mL of anhydrous ethanol. In the event that the α -halo ketone was a salt, then pyridine (1.2 eq) was also added to the vial. The vial was capped tightly and shaken in a heating block overnight at 82 °C. The reaction mixture was concentrated down and taken up in 2 mL of dichloromethane and 2 mL of water. It was basified with triethylamine (~10 drops) and extracted twice with dichloromethane. The organic layers were combined and concentrated to dryness, and the crude residue was dissolved in hot DMSO. The compound was purified optionally by chromatography, recrystallization, or by Gilson HPLC to yield the desired thiazole derivative.

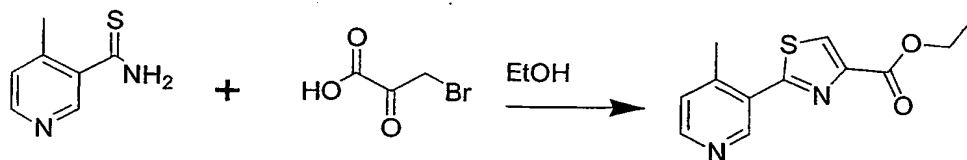
General Method P: Salt Formation



A solution of the pyridyl thiazole derivative (3.5 mmol) in Et₂O (50 mL) was treated dropwise at rt with an ethereal solution of a protic acid (4.4 mmol). A solid formed immediately and the reaction was stirred 1.5 h. The solid was collected by filtration and washed with Et₂O (2 x 50 mL). Drying under vacuum gave the desired salt.

Example 13

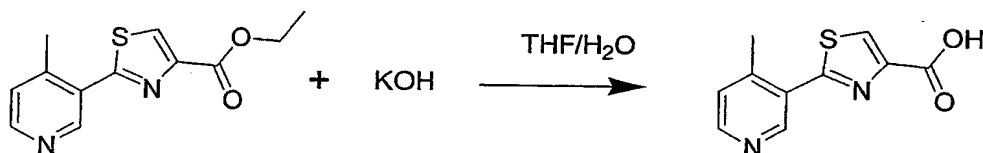
Preparation of 4-Methyl-3-[4-(1-piperidinylcarbonyl)-1,3-thiazol-2-yl]pyridine



Step 1. Preparation of Ethyl 2-(4-methyl-3-pyridinyl)-1,3-thiazole-4-carboxylate:

Bromopyruvic acid 4.09 g (0.0245 mmol) was diluted with ethanol (100 mL). Solid 4-methyl-3-pyridinecarbothioamide (2.86 g, 18.8 mmol) was added and the reaction mixture was heated at 82 °C overnight. After cooling to rt, triethylamine (2.47 g, 2.45 mmol) was added. The reaction mixture was adsorbed onto silica gel and purified by chromatography

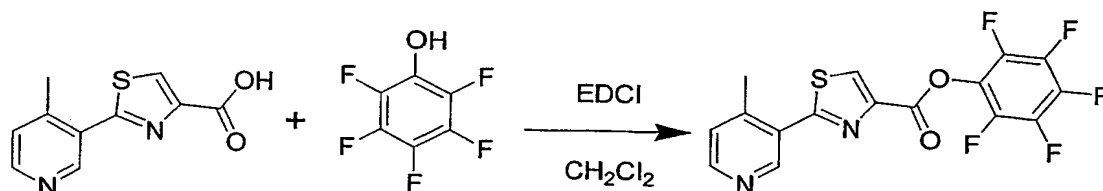
using 2% methanol in dichloromethane, yielding 3.33 g (55%) of the title compound as an off white solid: LCMS 249 ($M+H^+$), $t_R = 0.75$ min.



Step 2. Preparation of 2-(4-Methyl-3-pyridinyl)-1,3-thiazole-4-carboxylic acid:

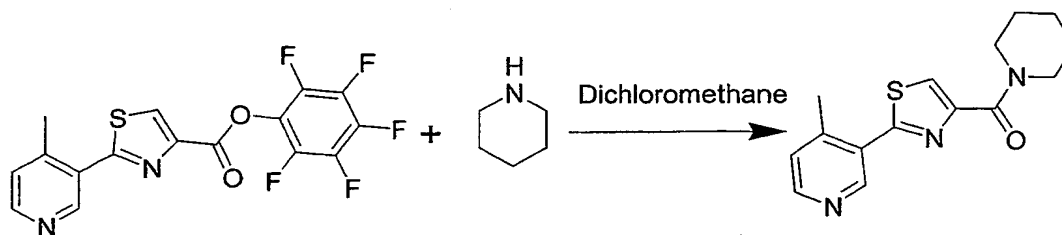
Ethyl 2-(4-methyl-3-pyridinyl)-1,3-thiazole-4-carboxylate 1.44 g (5.5 mmol) was dissolved in 40 mL of tetrahydrofuran. A solution of potassium hydroxide (0.962 g, 16.5 mmol) in water (10 mL) was added and the reaction mixture was heated at 70 °C under Ar for 1.5 h.

The reaction mixture was cooled, water was added, then the THF was removed under vacuum. The residue was then partitioned between dichloromethane and water. The organic layer, presumed to contain traces of unreacted starting material, was discarded. The aqueous layer was brought to pH 2 using 5% aqueous HCl. The material did not extract into ethyl acetate or dichloromethane. The product was precipitated from the aqueous layer using ether, then collected by filtration. The material obtained contained about three equivalents of KCl: yield 1.49 g (63%); white solid; LCMS ($M+H^+$) 221, $t_R = 0.69$ min.



Step 3: Preparation of 2, 3, 4, 5, 6-Pentafluorophenyl 2-(4-methyl-3-pyridinyl)-1,3-thiazole-4-carboxylate:

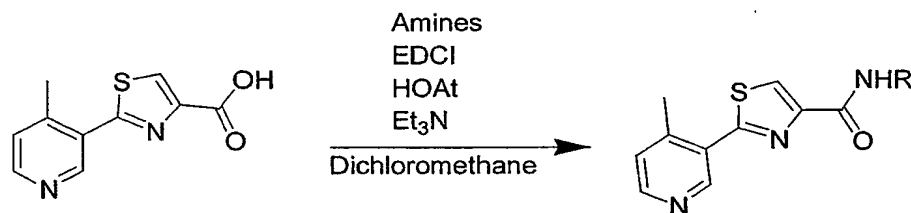
2-(4-Methyl-3-pyridinyl)-1,3-thiazole-4-carboxylic acid*3KCl 1.92 g (4.3 mmol) was suspended in dichloromethane (20 mL). Pentafluorophenol (1.40 g, 7.5 mmol) and EDCI (1.44 g, 8.25 mmol) were then added. The reaction mixture became homogenous upon the addition of triethylamine (2.3 g, 2.25 mmol). After stirring at rt overnight under Ar, dichloromethane and water were added. The material was partitioned between the two layers. The separated organic layer was washed three times with aqueous sodium carbonate solution followed by brine, then dried over sodium sulfate. Filtration and concentration afforded 100 mg of white solid (3.4%): LCMS ($M+H^+$) 387, $t_R = 2.60$ min.



Step 4. Preparation of 4-Methyl-3-[4-(1-piperidinylcarbonyl)-1,3-thiazol-2-yl]pyridine:

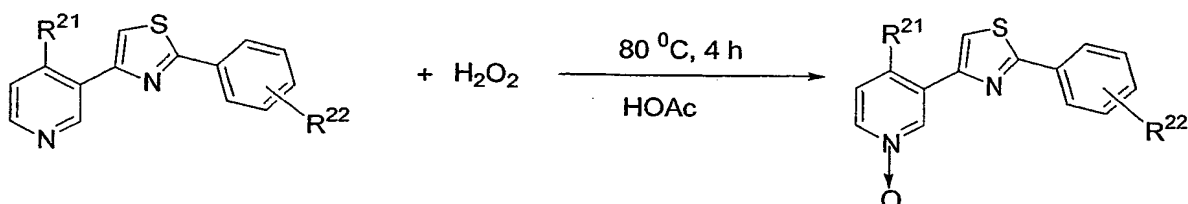
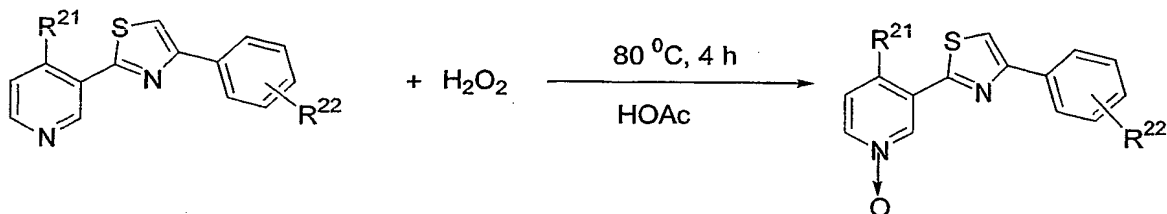
2, 3, 4, 5, 6-Pentafluorophenyl 2-(4-methyl-3-pyridinyl)-1,3-thiazole-4-carboxylate (97mg, 0.25 mmol) was dissolved in dichloromethane. Piperidine (64 mg, 0.5mmol) was added and the reaction mixture was stirred under Ar at rt for 2 h. The reaction mixture was then concentrated and purified by preparative TLC, using 5% (2N ammonia in methanol) / dichloromethane as eluent: yield 7%; brown oil; R_f 0.16 (70% EtOAc/hexanes) LCMS (M+H⁺) 288, t_R = 1.10 min.

General Method Q: Preparation of 2-(4-methyl-3-pyridinyl)-1,3-thiazole-4-carboxamides:



Amines (1.5 mmol) were weighed into EPA vials. A stock suspension of 4-methyl-3-pyridinyl)-1,3-thiazole-4-carboxylic acid * 3KCl (801 mg, ~ 1.8 mmol) was prepared by suspending it in dichloromethane (60 mL). N-Hydroxyazatriazole (0.280 g, 21.6mmol) was added to each vial, followed by EDCI (0.438 g, 21.6 mmol) and triethylamine (0.55 g, 54 mmol). After stirring at rt for 30 min, 5 mL of stock solution was added to each vial. The reaction mixture was stirred at rt overnight. The products were purified by a variety of methods including, preparatory TLC, flash chromatography using the Biotage, or Gilson HPLC.

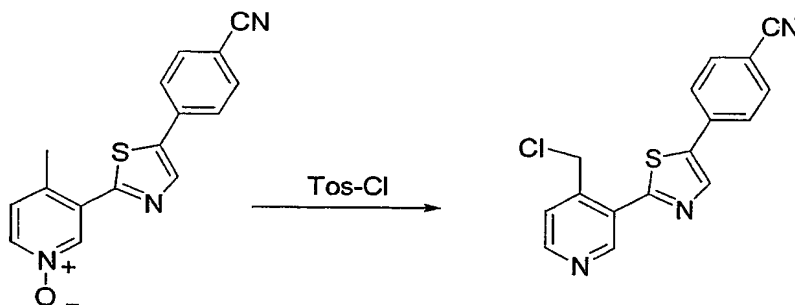
General Method R: Synthesis of Pyridine n-Oxides.



In a 25 mL flask, 1.39 g thiazole (0.005 mol) was mixed with 10 mL HOAc. After the mixture was cooled in ice bath, 1 mL H₂O₂ (about 0.017 mol) was added slowly with syringe. After the addition, the mixture was heated at 80 °C for 4 h then cooled to rt. Distilled water was added into the reaction mixture gradually till a lot of gray precipitate formed inside the solution. The precipitate was collected by filtration and washed with small amount of cold water. The product was dried in a vacuum oven, providing the target pyridine n-oxides. Yields averaged about 80%.

Example 14

Preparation of 2-(4-Chloromethyl-3-pyridyl)-4-(4-cyanophenyl)thiazole

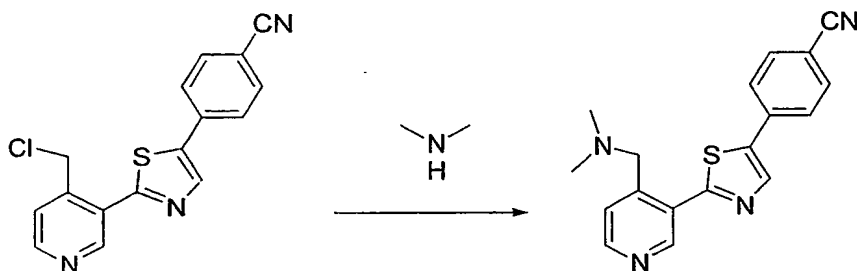


A mixture of the n-oxide (0.24 mmol) and tosyl chloride (0.26 mmol) in dioxane (5 mL) was heated to 80 °C and stirred for 3 h. The reaction mixture was evaporated to dryness and

purified by silica gel chromatography. LCMS and ^1H NMR were consistent with the formation of the title compound (0.14 mmol, 58%).

Example 15

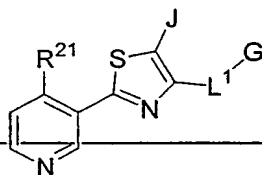
5 General Method S, as Exemplified by the Preparation of 2-(4-((dimethylamino)-3-pyridyl)-4-(4-cyanophenyl) thiazole.



- 10 A mixture of 2-(4-chloromethyl-3-pyridyl)-4-(4-cyanophenyl) thiazole (0.052 mmol) and dimethyl amine (0.70 mmol) in THF was heated to 50 °C for 8 h. The mixture was evaporated to dryness and purified by silica gel column chromatography, providing the 0.021 mmol (40%) of the title compound: R_f 0.15 (60% EtOAc/hexane); LCMS $(\text{M}+\text{H})^+$ 321.4. ^1H NMR was consistent with the assigned structure.

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Table II 2-(3-Pyridyl) thiazoles



Ex. No.	$\text{R}^{21\text{c}}$	J	L^1	G^c	Salt	$t_{\text{R}}^{\text{a,b}}$ min	MS $^{\text{a,b}}$ ($\text{M}+\text{H}^+$)	TLC R_f d(Solvent)	General Method
16	4-t-Bu	H	Bond	4- NO_2 Ph				0.80 (EtOAc)	O
17	4-iPr	H	Bond	3- NO_2 Ph			326.2	0.60 (50% EtOAc/ Hex)	N
18	4-Et	H	Bond	3-CN Ph			292.2	0.50 (50% EtOAc/ Hex)	N
19	4-Et	H	Bond	2- NO_2 Ph			312.2	0.50 (50% EtOAc/ Hex)	N
20	4-Et	H	Bond	3- NO_2 Ph			312.1	0.50 (50% EtOAc/ Hex)	N
21	4-Me	H	Bond	3- NO_2 Ph		2.44	298.1	0.18 (50% EtOAc/ Hex)	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
22	4-Et	H	Bond	3-thienyl	HBr	2.45			O
23	4-Me	H	Bond	2-thiophenecarbonitrile	TFA	2.22	284	0.13 (40% EtOAc/ Hex)	O
24	4-CyPr	H	Bond	3-NO ₂ Ph		2.48	324.2	0.06 (20% EtOAc/ Hex)	O
25	4-Me	H	Bond	2,4-diMeO Ph	TFA	3.05	313.2	0.34 (40% EtOAc/ Hex)	O
26	4-Me	H	Bond	2-NO ₂ Ph		2.12	298.1	0.15 (40% EtOAc/ Hex)	O
27	4-CyPr	H	Bond	4-Cl-3-NO ₂ Ph			358.2	0.50 (50% EtOAc/ Hex)	N
28	4-Me	H	Bond	3,4-diF Ph		2.57	289.2	0.24 (40% EtOAc/ Hex)	O
29	4-Me	H	Bond	3-MeO Ph		2.38	283.2	0.26 (30% EtOAc/ Hex)	O
30	4- <i>i</i> Pr	H	Bond	3-pyridinyl		1.32	282.3	0.25 3% (2M NH ₃ in MeOH)/CH ₂ Cl ₂	O
31	4-Me	H	Bond	5-Cl thien-2-yl	HCl	2.70	293.3	0.40 (40% EtOAc/ Hex)	O
32	4-Me	H	CH ₂	4-Me Ph				0.32 (40% EtOAc/ Hex)	M
33	4-Me	H	Bond	3-CN Ph		2.25	278.29	0.24 (50% EtOAc/ Hex)	O
34	4-Pr	H	Bond	2-F Ph				0.79 (50% EtOAc/ Hex)	O
35	4-Pr	H	Bond	Ph				0.77 (50% EtOAc/ Hex)	O
36	4-Me	H	Bond	4-Cl Ph	HCl		287	0.33 (25% EtOAc/ Hex)	O
37	4-CyPr	H	Bond	Ph		2.35	279.2	0.14 (20% EtOAc/ Hex)	O
38	4-CyPr	H	Bond	2-NO ₂ Ph			324.2	0.55 (50% EtOAc/ Hex)	N
39	4-Me	H	Bond	4-Br Ph				0.30 (40% EtOAc/ Hex)	O
40	4-Et	H	Bond	4-Me Ph			281.3	0.55 (50% EtOAc/ Hex)	N
41	4-Pr	H	Bond	2-NO ₂ Ph				0.70 (50% EtOAc/ Hex)	O
42	4-CyPr	H	Bond	4-F Ph			297.3	0.55 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
43	4-Pr	H	Bond	4-F Ph				0.77 (50% EtOAc/ Hex)	O
44	4-Et	H	Bond	3-F Ph			285.2	0.55 (50% EtOAc/ Hex)	N
45	4-Et	H	Bond	2,3-dihydro-1,4-benzodioxin-6-yl)			339.3	0.55 (50% EtOAc/ Hex)	N
46	4-Me	H	Bond	Ph		2.36	253.3	0.36 (25% EtOAc/ Hex)	O
47	4-Me	H	Bond	2,4-diMe Ph	HBr	2.62	281.3	0.39 (40% EtOAc/ Hex)	O
48	4-Me	H	Bond	4-F Ph		2.43	271.2	0.18 (40% EtOAc/ Hex)	O
49	4-Me	H	Bond	5-Cl thien-2-yl		2.73	293.1	0.29 (40% EtOAc/ Hex)	O
50	4-Me	H	O	cyclopentyl		2.21	261	0.50 (50% EtOAc/ Hex)	K
51	4-Pr	H	Bond	3-CN Ph				0.53 (100% EtOAc)	O
52	4-Et	H	Bond	4-Cl-3-NO ₂ Ph			346.1	0.55 (50% EtOAc/ Hex)	N
53	4-Me	H	Bond	4-MeO Ph			283	0.30 (25% EtOAc/ Hex)	O
54	4- <i>i</i> Pr	H	Bond	2-NO ₂ Ph			326.3	0.60 (50% EtOAc/ Hex)	N
55	4-Et	H	Bond	4-Cl Ph	MS A	2.84	301.2	---	O/X
56	4-Et	Me	Bond	Ph			281.2	0.55 (50% EtOAc/ Hex)	N
57	4-Et	H	Bond	Ph			267.2	0.65 (50% EtOAc/ Hex)	N
58	4-Me	H	Bond	4-Cl Ph			287	0.33 (25% EtOAc/ Hex)	O
59	4-Me	H	Bond	t-Bu		2.31	233	0.55 (50% EtOAc/ Hex)	G
60	4-CyPr	H	Bond	3-pyridinyl		0.81	280.2	0.36 (100% EtOAc)	O
61	4-Me	H	O	cyclohexyl		2.47	275	0.6 (50% EtOAc/ Hex)	K
62	4-CyPr	H	Bond	4-NO ₂ Ph		2.51	324.2	0.06 (20% EtOAc/ Hex)	O
63	4-CyPr	H	Bond	2,4-diMe Ph			307.2	0.50 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
								EtOAc/ Hex)	
64	4-Et	H	Bond	2-MeO Ph			297.2	0.55 (50% EtOAc/ Hex)	N
65	4-Pr	H	Bond	4-Me Ph				0.78 (100% EtOAc)	O
66	4-Et	H	Bond	cyclohexyl			273.3	0.65 (50% EtOAc/ Hex)	N
67	4- <i>i</i> Pr	H	Bond	Ph			281.2	0.40 (30% EtOAc/ Hex)	N
68	4-Me	H	OCH ₂	Ph		2.29	283	0.35 (50% EtOAc/ Hex)	K
69	4-Me	H	Bond	1-cyclopenten-1-yl		2.39	243	0.5 (50% EtOAc/ Hex)	G
70	4-Me	H	Bond	cycloheptyl		2.72	273	0.29 (25% EtOAc/ Hex)	G
71	4-Me	H	O	(2R)-bicyclo[2.2.1]hept-2-yl		2.53	287	0.5 (50% EtOAc/ Hex)	K
72	4-CyPr	H	Bond	2-MeO Ph			309.2	0.50 (50% EtOAc/ Hex)	N
73 wlf	4-Pr	H	Bond	4-CF ₃ Ph				0.75 (100% EtOAc)	O
74	4-CyPr	H	Bond	3-F Ph		2.48	297.2	0.11 (20% EtOAc/ Hex)	O
75	4-Et	H	Bond	2-Cl Ph			301.2	0.60 (50% EtOAc/ Hex)	N
76	4-Me	H	O	<i>i</i> Pr		1.99	235	0.28 (25% EtOAc/ Hex)	I
77	4-Me	H	Bond	3-Br thien-2-yl	TF A	2.62	339.6	0.34 (40% EtOAc/ Hex)	O
78	4-Me	H	Bond	cyclopentyl		2.29	245	0.11 (20% EtOAc/ Hex)	G
79	4-Me	H	CH ₂	4-Cl Ph		2.56	301.3	0.24 (40% EtOAc/ Hex)	M
80	4- <i>i</i> Pr	H	Bond	3-F Ph			299.5	0.55 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
81	4- <i>i</i> Pr	H	Bond	4-Me pyridin-3-yl	2 TF A	2.70		0.55 (50% EtOAc/ Hex)	O
82	4-Me	H	O	cycloheptyl		2.57	289	0.66 (50% EtOAc/ Hex)	K
83	4- <i>i</i> Pr	H	Bond	4-NO ₂ Ph			326.3	0.60 (50% EtOAc/ Hex)	N
84	4-Pr	H	Bond	3-NO ₂ Ph				0.69 (100% EtOAc)	O
85	4-Me	H	Bond	4-NO ₂ Ph	TF A	2.38	298.3	0.17 (40% EtOAc/ Hex)	O
86	4-Et	H	Bond	2,4-diMe Ph			294.2	0.55 (50% EtOAc/ Hex)	N
87	4-Me	H	Bond	cyclohexyl		2.63	259	0.33 (33% EtOAc/ Hex)	G
88	4-Et	H	Bond	4-F Ph			285.2	0.60 (50% EtOAc/ Hex)	N
89	4-Me	H	Bond	4-NO ₂ Ph		2.34	298.2	0.20 (40% EtOAc/ Hex)	O
90	4-CyPr	H	Bond	3-thienyl	HBr	2.29		0.55 (50% EtOAc/ Hex)	O
91	4-Et	H	Bond	4-NO ₂ Ph			312.2	0.45 (50% EtOAc/ Hex)	N
92	4-Me	H	Bond	3-Cl Ph		2.66	287.29	0.32 (50% EtOAc/ Hex)	O
93	4- <i>t</i> -Bu	H	Bond	4-F Ph				0.80 (50% EtOAc/ Hex)	O
94	4- <i>i</i> Pr	H	Bond	3-Cl Ph			315.6	0.50 (50% EtOAc/ Hex)	N
95	4-Me	H	Bond	3-Cl thien- 2-yl	TF A		256	0.34 (40% EtOAc/ Hex)	O
96	4-Me	H	Bond	3-F Ph		2.44	271.27	0.23 (50% EtOAc/ Hex)	O
97	4-Pr	H	Bond	2-naphthyl				0.75 (100% EtOAc)	O
98	4-Et	H	Bond	4-MeO Ph			297.2	0.60 (50% EtOAc/ Hex)	N
99	4- <i>t</i> -Bu	H	Bond	4-Me Ph				0.83 (100% EtOAc)	O
100	4-Me	H	Bond	3-pyridinyl		0.64	254.4	0.13 (3% MeOH/ CH ₂ Cl ₂)	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
101	4-t-Bu	H	Bond	4-MeO Ph				0.83 (100% EtOAc)	O
102	4-Et	H	Bond	3-Cl Ph			301.2	0.50 (50% EtOAc/ Hex)	N
103	4-Pr	H	Bond	3-Cl Ph				0.74 (100% EtOAc)	O
104	4-Et	H	Bond	3-Br Ph			345.2	0.50 (50% EtOAc/ Hex)	N
105	4-t-Bu	H	Bond	3-NO ₂ Ph				0.74 (100% EtOAc)	O
106	4-iPr	H	Bond	2-MeO Ph			311.3	0.55 (50% EtOAc/ Hex)	N
107	4-iPr	H	Bond	3,4-diF Ph			317.5	0.50 (50% EtOAc/ Hex)	N
108	4-t-Bu	H	Bond	Ph		2.96	295.1	0.82 (100% EtOAc)	O
109	4-Pr	H	Bond	4-Cl Ph		3.15	315	0.74 (100% EtOAc)	N
110	4-Et	H	Bond	2,5-diMeO Ph			327.2	0.50 (50% EtOAc/ Hex)	N
111	4-Me	H	Bond	4-pyridinyl	2 TF A	0.77	254	0.19 (3% MeOH/ CH ₂ Cl ₂)	O
112	4-Pr	H	Bond	3-Br Ph		2.05	361.2	0.77 (100% EtOAc)	O
113	4-t-Bu	H	Bond	4-Cl-3-NO ₂ Ph		3.22	374.2	0.78 (100% EtOAc)	O
114	4-iPr	H	Bond	2,4-diMe Ph			309.7	0.50 (50% EtOAc/ Hex)	N
115	4-Me	H	Bond	4-COOH Ph	NH ₄ Cl	2.30	295.97	0.48 (10% MeOH/ CH ₂ Cl ₂)	O
116	4-Me	H	Bond	3-Br Ph		2.73	331.28	0.25 (50% EtOAc/ Hex)	O
117	4-Me	H	OCH ₂	exo/endo norbornyl		2.74	301	0.54 (50% EtOAc/ Hex)	K
118	4-t-Bu	H	Bond	2-Br Ph		3.07	312.9	0.78 (100% EtOAc)	O
119	4-iPr	H	Bond	4-pyridinyl	2 TF A	0.99	282	0.27 (3% MeOH/ CH ₂ Cl ₂)	O
120	4-iPr	H	Bond	3-CN Ph			306.6	0.50 (50% EtOAc/ Hex)	N
121	4-iPr	H	Bond	7-heptyl		3.03	301	0.65 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
122	4-CyPr	H	Bond	4-Cl Ph			313.6	0.40 (30% EtOAc/ Hex)	N
123	4-Pr	H	Bond	4-MeO Ph		1.29	311.3	0.76 (100% EtOAc)	O
124	4- <i>i</i> Pr	H	Bond	4-Cl-3-NO ₂ Ph			360.8	0.55 (50% EtOAc/ Hex)	N
125	4-CyPr	H	Bond	4-cyclohexyl			285.2	0.65 (50% EtOAc/ Hex)	
126	4- <i>t</i> -Bu	H	Bond	2-Cl Ph		3.14	328.9	0.84 (100% EtOAc)	O
127	4- <i>i</i> Pr	H	Bond	3-thienyl	HBr	2.61			O
128	4-Pr	H	Bond	5-Me-3-Ph-4-isoxazolyl		1.33	362.3	0.72 (100% EtOAc)	O
129	4- <i>i</i> Pr	H	Bond	4-MeO Ph			311.2	0.40 (30% EtOAc/ Hex)	N
130	4- <i>t</i> -Bu	H	Bond	3-CN Ph		3.00	319.9	0.77 (100% EtOAc)	O
131	4-Pr	H	Bond	2-MeO Ph		1.33	311.3	0.78 (100% EtOAc)	O
132	4-CyPr	H	Bond	4-MeO Ph			309.2	0.40 (30% EtOAc/ Hex)	N
133	4-Me	H	Bond	2-MeO Ph	TF A	3.02	283.3	0.29 (40% EtOAc/ Hex)	O
134	4- <i>i</i> Pr	H	Bond	4-F Ph			299.3	0.60 (30% EtOAc/ Hex)	N
135	4-Me	H	O	cyclobutyl		1.94	247	0.55 (50% EtOAc/ Hex)	I
136	4-Pr	H	Bond	4-(diFMeO) Ph		1.28	347.3	0.78 (100% EtOAc)	O
137	4- <i>t</i> -Bu	H	Bond	4-CN Ph		2.96	319.9	0.77 (100% EtOAc)	O
138	4-Et	H	Bond	4-CN Ph			292.2	0.50 (50% EtOAc/ Hex)	N
139	4-Et	H	Bond	4-(diFMeO) Ph			333.2	0.55 (50% EtOAc/ Hex)	N
140	4-CyPr	H	Bond	2-F Ph			297.2	0.60 (50% EtOAc/ Hex)	N
141	4- <i>t</i> -Bu	H	Bond	3-F Ph		3.11	312.9	0.55 (50% EtOAc/ Hex)	O
142	4- <i>t</i> -Bu	H	Bond	2,4-diMe Ph		3.55	323	0.83 (100% EtOAc)	O
143	4- <i>t</i> -Bu	Me	Bond	Ph		3.00	308.5	0.79 (100% EtOAc)	J
144	4-Me	Me	Bond	4-Cl Ph			301	0.33 (25% EtOAc/ Hex)	J
145	4- <i>i</i> Pr	H	Bond	2,5-diMeO			341.6	0.50 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
				Ph				EtOAc/ Hex)	
146	4- <i>i</i> Pr	H	Bond	4-Me Ph			295.3	0.60 (50% EtOAc/ Hex)	N
147	4-Pr	H	Bond	4-Br Ph		3.18	361.2	0.76 (100% EtOAc)	O
148	4-Pr	H	Bond	2-Cl Ph		3.00	315.3	0.55 (50% EtOAc/ Hex)	O
149	4- <i>t</i> -Bu	H	Bond	4-(diFMeO) Ph		3.11	361.3	0.83 (100% EtOAc)	O
150	4- <i>t</i> -Bu	H	Bond	2-MeO Ph		3.00	325	0.83 (100% EtOAc)	O
151	4- <i>t</i> -Bu	H	Bond	3,4-diCl Ph		3.51	363.2	0.77 (100% EtOAc)	O
152	4-Et	H	Bond	4-CF ₃ Ph			335.2	0.50 (50% EtOAc/ Hex)	N
153	4- <i>i</i> Pr	H	Bond	cyclohexyl		2.88	287	0.48 (25% EtOAc/ Hex)	G
154	4-Et	H	Bond	4-Cl Ph			301.2	0.60 (50% EtOAc/ Hex)	N
155	4-Et	H	Bond	2-F Ph			285.2	0.60 (50% EtOAc/ Hex)	N
156	4- <i>i</i> Bu	H	Bond	4-Cl Ph		3.37	329	0.45 (50% EtOAc/ Hex)	N
157	4-Pr	H	Bond	2,4-diMe Ph		1.36	309.3	0.77 (100% EtOAc)	O
158	4- <i>i</i> Pr	H	Bond	cyclopentyl		2.66	273	0.63 (50% EtOAc/ Hex)	G
159	4- <i>t</i> -Bu	H	Bond	3-Cl Ph		3.55	329	0.81 (100% EtOAc)	O
160	4-Me	H	Bond	4-Cl-3-NO ₂ Ph		2.62	332.2	0.35 (50% EtOAc/ Hex)	O
161	4-Et	Me	Bond	4-Cl Ph			315.2	0.55 (50% EtOAc/ Hex)	N
162	4-CyPr	H	Bond	3-Br Ph				0.55 (50% EtOAc/ Hex)	N
163	4- <i>i</i> Pr	H	O	<i>i</i> Pr		2.29	263	0.50 (50% EtOAc/ Hex)	I
164	4-Me	H	Bond	2-naphthyl		2.81	303.2	0.32 (40% EtOAc/ Hex)	O
165	4-Me	H	Bond	2-Cl Ph		2.43	287.3	0.48 (50% EtOAc/ Hex)	O
166	4-Et	H	Bond	4-Br Ph			245.2	0.55 (50% EtOAc/ Hex)	N
167	4-Me	H	Bond	4-(diFMeO) Ph		2.49	319.3	0.20 (50% EtOAc/ Hex)	O
168	4-CyPr	Me	Bond	Ph			293.2	0.60 (50% EtOAc/ Hex)	N
169	4-Me	H	Bond	3,5-diCF ₃				0.30 (40% EtOAc/ Hex)	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
				Ph				EtOAc/ Hex)	
170	4-CyPr	H	Bond	4-Me Ph		2.56	293.2	0.15 (20% EtOAc/ Hex)	O
171	4- <i>i</i> Pr	H	Bond	4-Cl Ph			315.6	0.50 (30% EtOAc/ Hex)	N
172	4-CyPr	H	Bond	2,5-diMeO Ph			339.2	0.50 (50% EtOAc/ Hex)	N
173	4-CyPr	H	Bond	3-Cl Ph		2.69	313.1	0.12 (20% EtOAc/ Hex)	O
174	4-CyPen	H	Bond	3-NO ₂ Ph			352.3	0.50 (50% EtOAc/ Hex)	N
175	4-Me	H	Bond	2,4-diCl Ph		2.73	321	0.35 (50% EtOAc/ Hex)	O
176	4- <i>i</i> Pr	H	Bond	2-Cl Ph			315.6	0.50 (50% EtOAc/ Hex)	N
177	4-CyPr	H	Bond	4-pyridinyl		0.75	280.2	0.34 (50% EtOAc/ Hex)	O
178	H	H	CH ₂	4-Cl Ph			287	0.27 (25% EtOAc/ Hex)	M
179	4-Pr	H	Bond	4-NO ₂ Ph		1.31	326.2	0.70 (100% EtOAc)	O
180	4-Et	H	Bond	1-adamantyl			325.4	0.50 (50% EtOAc/ Hex)	N
181	4- <i>i</i> Pr	H	Bond	3,4-diCl Ph			349.2	0.50 (50% EtOAc/ Hex)	N
182	4-Me	H	Bond	2,4-diCl Ph	HCl		321	0.42 (5% MeOH/ CH ₂ Cl ₂)	O
183	4-Me	H	Bond	N,N-diethyl-3-aniline				0.65 (100% EtOAc)	Y
184	4-Bu	H	Bond	4-Cl Ph		3.24	329	0.38 (10% EtOAc/ CH ₂ Cl ₂)	N
185	H	H	CH ₂	4-Me Ph			267	0.41 (25% EtOAc/ Hex)	M
186	4-Me	H	Bond	2-F Ph		2.48	271.27	0.45 (50% EtOAc/ Hex)	O
187	4- <i>t</i> -Bu	H	Bond	4-Cl Ph		3.25	328.9	0.82 (100% EtOAc)	O
188	4- <i>t</i> -Bu	H	Bond	4-CF ₃ Ph		3.36	363.2	0.83 (100% EtOAc)	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
189	4-CyPen	H	Bond	3-F Ph			325.3	0.60 (50% EtOAc/ Hex)	N
190	4-Ph	H	Bond	4-F Ph			333.4	0.55 (50% EtOAc/ Hex)	N
191	H	H	CH ₂	4-Br Ph			330	0.36 (25% EtOAc/ Hex)	M
192	4-t-Bu	H	Bond	4-Br Ph		3.29	373.2	0.83 (100% EtOAc)	O
193	4-CyPr	H	Bond	4-Me-3-pyridinyl		0.79	294.2	0.30 (100% EtOAc)	O
194	4-Pr	H	Bond	t-Bu		1.38	261.3	0.90 (100% EtOAc)	G
195	4-t-Bu	H	Bond	3-Br Ph		3.29	373.2	0.83 (100% EtOAc)	O
196	4-t-Bu	Me	Bond	4-Br Ph		3.25	387.2	0.82 (100% EtOAc)	W
197	4-iPr	H	Bond	4-Br Ph			359.2	0.60 (50% EtOAc/ Hex)	N
198	H	H	Bond	CyBu		2.75	231	0.24 (25% EtOAc/ Hex)	G
199	4-Et	H	Bond	2,4-diCl Ph			335.2	0.50 (50% EtOAc/ Hex)	N
200	4-Pr	H	Bond	4-CN Ph		1.37	357.3	0.71 (100% EtOAc)	O
201	4-CyPen	H	Bond	2-NO ₂ Ph				0.55 (50% EtOAc/ Hex)	N
202	4-Me	H	Bond	4-CN Ph		2.89	278.3	0.17 (40% EtOAc/ Hex)	O
203	4-Me	H	Bond	1-adamantyl		3.16	311	0.47 (50% EtOAc/ Hex)	G
204	4-Et	Me	Bond	4-MeO-Ph			311.2	0.50 (50% EtOAc/ Hex)	N
205	4-t-Bu	H	Bond	2-NO ₂ Ph		2.81	339.9	0.71 (100% EtOAc)	O
206	4-iPr	H	Bond	t-Bu		2.76	261	0.50 (25% EtOAc/ Hex)	G
207	H	H	CH ₂	3-Cl Ph			287	0.32 (25% EtOAc/ Hex)	M
208	piperid inyl	H	Bond	3-Cl Ph		2.31	356.3	0.06 (20% EtOAc/ Hex)	L
209	4-Me	H	Bond	4-(trifluoromethoxy)Ph		2.8	337.3	0.50 (50% EtOAc/ Hex)	O
210	4-Et	H	Bond	3,4-diCl Ph			335.2	0.55 (50% EtOAc/ Hex)	N
211	4-CyPen	H	Bond	3-CN Ph			332.2	0.50 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
212	4- <i>i</i> Bu	H	Bond	CyHex		3.75	301	0.70 (50% EtOAc/ Hex)	W
213	4- <i>i</i> Pr	H	Bond	4-CN Ph			306.6	0.55 (50% EtOAc/ Hex)	N
214	4- <i>i</i> Pr	H	Bond	4-(diFMeO) Ph			347.7	0.50 (50% EtOAc/ Hex)	N
215	4- <i>t</i> -Bu	Me	Bond	4-MeO Ph		2.96	339	0.75 (100% EtOAc)	W
216	4-F Ph	H	Bond	3-NO ₂ Ph		3.26	378.2	0.81 (100% EtOAc)	O
217	H	H	CH ₂	3-Me Ph			267	0.39 (25% EtOAc/ Hex)	M
218	4- <i>i</i> Pr	H	Bond	2-naphthyl			331.6	0.50 (50% EtOAc/ Hex)	N
219	4-F Ph	H	Bond	3-Cl Ph		3.49	367.3	0.50 (50% EtOAc/ Hex)	O
220	4-CyPr	H	Bond	2-naphthyl			329.2	0.55 (50% EtOAc/ Hex)	N
221	4-Et	H	Bond	4-(trifluoromethoxy)Ph			351.2	0.55 (50% EtOAc/ Hex)	N
222	4- <i>i</i> Pr	H	Bond	2-pyridinyl	2 TF A	1.8	282.2	0.27 (3% MeOH/ CH ₂ Cl ₂)	O
223	4- <i>t</i> -Bu	H	Bond	2,4-diCl Ph		3.47	363.1	0.83 (100% EtOAc)	O
224	4- <i>i</i> Pr	H	Bond	1-cyclopenten-1-yl		2.76	270	0.60 (50% EtOAc/ Hex)	G
225	4-Ph	H	Bond	3-NO ₂ Ph		3.16	360.2	0.68 (50% EtOAc/ Hex)	O
226	4-CyPr	H	Bond	4-Br Ph		2.82	357.1	0.15 (20% EtOAc/ Hex)	O
227	4-F Ph	H	Bond	3-CN Ph		3.13	358.3	0.60 (50% EtOAc/ Hex)	O
228	H	H	O	cycloheptyl		2.89	275	0.66 (50% EtOAc/ Hex)	K
229	4- <i>i</i> Pr	H	Bond	2-F Ph			299.7	0.50 (50% EtOAc/ Hex)	N
230	4-Me	H	Bond	4-CN Ph	MS A			0.50 (50% EtOAc/ Hex)	O/P
231	4-Ph	H	Bond	4-Me Ph		3.24	329.3	0.74 (100% EtOAc)	O
232	4-Me	I	Bond	4-Cl Ph		3.23	413	0.50 (50% EtOAc/ Hex)	X
233	4-F Ph	H	Bond	3-F Ph		3.3	351.3	0.73 (50% EtOAc/ Hex)	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
234	4-CyPen	H	Bond	4-NO ₂ Ph		3.11	352.3	0.53 (50% EtOAc/ Hex)	N
235	4-morpholinyl Me	H	Bond	4-CN Ph				0.76 (10% 2M NH ₃ in MeOH/ EtOAc)	S
236	4-Ph	H	Bond	Ph				0.50 (50% EtOAc/ Hex)	N
237	H	H	O	Exo-norborn-2-yl				0.50 (50% EtOAc/ Hex)	K
238	4-CyPr	H	Bond	4-(diFMeO) Ph				0.60 (50% EtOAc/ Hex)	N
239	H	H	Bond	t-Bu				0.50 (50% EtOAc/ Hex)	G
240	4-t-Bu	H	Bond	2-Me-3-pyridinyl				0.15 (100% EtOAc)	O
241	4-Me	H	Bond	2-pyridinyl				0.50 (5% MeOH/ CH ₂ Cl ₂)	O
242	4-CyPr	H	Bond	4-CN Ph				0.55 (50% EtOAc/ Hex)	N
243	4-Et	Me	Bond	4-Br Ph				0.55 (50% EtOAc/ Hex)	N
244	4-Me	H	carbox-amide	N-piperidin-1-yl				0.17 (3% MeOH/ CH ₂ Cl ₂)	Q
245	4-Pr	Me	Bond	4-Br Ph				0.77 (100% EtOAc)	O
246	4-CyPr	H	Bond	4-CF ₃ Ph				0.60 (50% EtOAc/ Hex)	N
247	H	H	O	cyclohexyl				0.50 (50% EtOAc/ Hex)	K
248	4-CyPr	Me	Bond	4-Cl Ph				0.60 (50% EtOAc/ Hex)	N
249	H	H	Bond	ethyl 3-methylbutanoate				0.50 (50% EtOAc/ Hex)	G
250	4-Me	H	Bond	4-CN Ph	MS A			0.50 (50% EtOAc/ Hex)	O/X
251	4-Ph	H	Bond	3-CN Ph				0.50 (50% EtOAc/ Hex)	O
252	4-Me	H	Bond	4-CN Ph	HCl			0.50 (50% EtOAc/ Hex)	O/X
253	4-Et	H	Bond	3-pyridinyl				0.50 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
254	4-Pr	H	Bond	3-phenyl benzoate		1.34	401.3	0.80 (100% EtOAc)	O
255	4-Me	I	Bond	cyclohexyl				0.50 (50% EtOAc/ Hex)	X
256	4-CyPen	H	Bond	3-Cl Ph				0.55 (50% EtOAc/ Hex)	N
257	4-Et	H	Bond	2-naphthyl				0.50 (50% EtOAc/ Hex)	N
258	4-t-Bu	H	Bond	4-(trifluoromethoxy)Ph				0.83 (100% EtOAc)	O
259	H	H	O	CyPen				0.50 (50% EtOAc/ Hex)	K
260	4-CyPr	H	Bond	3,4-diCl Ph				0.55 (50% EtOAc/ Hex)	N
261	H	H	Bond	1-adamantyl				0.50 (50% EtOAc/ Hex)	G
262	H	Me	Bond	Ph				0.44 (25% EtOAc/ Hex)	O
263	4-iPr	H	Bond	3-furanyl	TF A			0.50 (50% EtOAc/ Hex)	O
264	4-Me	H	Bond	4-CN Ph	mal eate			0.50 (50% EtOAc/ Hex)	O/P
265	4-Me	H	Bond	3,4-diCl Ph				0.50 (50% EtOAc/ Hex)	O
266	4-CyPr	H	Bond	4-CN Ph	MS A			0.50 (50% EtOAc/ Hex)	O/X
267	H	H	OCH ₂	Endo/Exo norbornyl				0.50 (50% EtOAc/Hex)	K
268	4-CyPr	H	Bond	2-Cl Ph				0.13 (20% EtOAc/ Hex)	O
269	4-Ph	H	Bond	3-F Ph				0.50 (50% EtOAc/ Hex)	O
270	H	Me	Bond	4-Cl Ph				0.34 (25% EtOAc/ Hex)	J
271	4-CyPr	Me	Bond	4-MeO Ph				0.55 (50% EtOAc/ Hex)	N
272	4-t-Bu	Me	Bond	3-Cl-4-Me Ph				0.75 (100% EtOAc)	O
273	4-Me	H	Carbonyl	Endo/exo N-norbornylamine		2.25	314	0.25 (3% MeOH/ CH ₂ Cl ₂)	Q
274	4-F Ph	H	Bond	4-F Ph				0.66 (50% EtOAc/ Hex)	O
275	4-F Ph	H	Bond	3,4-diCl Ph				0.50 (50% EtOAc/ Hex)	O

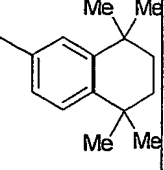
Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
								EtOAc/ Hex)	
276	4-CyPen	H	Bond	4-F Ph				0.60 (50% EtOAc/ Hex)	N
277	4-CyPen	H	Bond	3-Br Ph				0.55 (50% EtOAc/ Hex)	N
278	4-thiomorpholine	H	Bond	4-Cl Ph		3.21	333.3	0.59 (50% EtOAc/ Hex)	L
279	H	H	CH ₂	3,4-diCl Ph				0.27 (25% EtOAc/ Hex)	M
280	4-Me	H	Bond	2-pyridinyl	TF A	0.94	254.2	0.49 (5% 2M NH ₃ in MeOH/ CH ₂ Cl ₂)	O
281	4-Me	I	Bond	3,4-diF Ph		3.1	415	0.54 (50% EtOAc/ Hex)	
282	4-Me	H	NH	3,5-diCl Ph		2.9	336	0.63 (100% EtOAc)	H
283	4-N-morpholino	H	Bond	4-Cl Ph		2.07	358.3	0.36 (50% EtOAc/ Hex)	L
284	4-CyPen	H	Bond	4-MeO Ph				0.55 (50% EtOAc/ Hex)	N
285	4-iPr	Me	Bond	4-Br Ph					N
286	4-iPr	H	Bond	2,4-diCl Ph				0.40 (30% EtOAc/ Hex)	N
287	4-iPr	H	Bond	3-Ph benzoate					N
288	4-iPr	H	Bond	5-Me-3-Ph-4-isoxazolyl				0.53 (50% EtOAc/ Hex)	N
289	4-Ph	H	Bond	3-pyridinyl		1.91	316.09	0.22 (50% EtOAc/ Hex)	O
290	4-iPr	Me	Bond	4-Cl Ph				0.60 (50% EtOAc/ Hex)	N
291	4-Pr	Et	Bond	4-Cl Ph			344		W
292	4-(4-F Ph)	H	Bond	4-NO ₂ Ph		3.29	378.2	0.42 (50% EtOAc/ Hex)	O
293	H	H	CH ₂	4-F Ph				0.32 (25% EtOAc/ Hex)	M
294	4-CyPen	H	Bond	4-Me Ph				0.55 (50% EtOAc/ Hex)	N
295	4-CyPen	H	Bond	4-CF ₃ Ph				0.55 (50% EtOAc/ Hex)	N
296	H	H	Bond	4-pyridinyl	2 TF			0.45 (3% MeOH/	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
					A			CH ₂ Cl ₂)	
297	4-F Ph	H	Bond	4-diFMeO Ph				0.62 (50% EtOAc/ Hex)	O
298	4-CyPr	H	Bond	2-pyridinyl		1.04	280.2	0.31 (EtOAc)	O
299	4-Pr	H	Bond	4-CF ₃ O Ph		1.32	365.3	0.77 (EtOAc)	O
300	H	H	CH ₂	3-NO ₂ Ph				0.16 (25% EtOAc/ Hex)	M
301	4-Me	H	O	Et			221		I
302	4-(4-F Ph)	H	Bond	4-Cl Ph		3.48	367.3	0.69 (50% EtOAc/ Hex)	O
303	H	H	Bond	N,N-diEtN			234		H
304	4-Ph	H	Bond	2-NO ₂ Ph		2.92	360.08	0.65 (50% EtOAc/ Hex)	O
305	4-iPr	H	CH ₂	4-Cl Ph					N
306	H	H	Bond	2H-1,4-benzoxazin-3(4H)-one			310	0.11 (50% EtOAc/ Hex)	M
307	H	H	Bond	2-Ph benzoate			359	0.26 (25% EtOAc/ Hex)	O
308	4-CyPr	H	Bond	4-CN Ph	HCl			0.08 (20% EtOAc/ Hex)	O
309	4-CyPr	Me	Bond	4-Br Ph				0.60 (50% EtOAc/ Hex)	N
310	4-Ph	H	Bond	4-Cl Ph					N
311	4-Bu	Pr	Bond	4-Cl Ph					N
312	4-CyPr	H	Bond	1-adamantyl				0.55 (50% EtOAc/ Hex)	N
313	H	H	Bond	3-pyridinyl				0.50 (5% MeOH/ CH ₂ Cl ₂)	O
314	4-(4-F Ph)	H	Bond	4-CF ₃ Ph				0.69 (50% EtOAc/ Hex)	O
315	H	H	Bond	3-pyridinyl				0.50 (5% MeOH/ CH ₂ Cl ₂)	O
316	4-(4-F Ph)	H	Bond	4-CF ₃ Ph				0.69 (50% EtOAc/ Hex)	O
317	4-Ph	H	Bond	4-iPr pyridin-3-yl				0.21 (50% EtOAc/ Hex)	O
318	3-Me	H	Bond	1-adamantyl			311		G
319	4-(4-F Ph)	H	Bond	4-CN Ph				0.49 (50% EtOAc/ Hex)	O
320	4-iPr	H	Bond	1-adamantyl			339		G
321	H	H	Bond	1-CyPen-1-					G

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
				yl					
322	4-CyPen	H	Bond	4-Br Ph				0.55 (50% EtOAc/ Hex)	N
323	4-CyPen	H	Bond	4-Cl Ph				0.55 (50% EtOAc/ Hex)	N
324	4-Ph	H	Bond	4-pyridinyl					O
325	4-(4-pyridinyl)-1-piperazinyl	H	Bond	4-CN Ph	4 TF A			0.53 (10% 2M NH ₃ in MeOH/ EtOAc)	S
326	4-iPr	H	1Bond	2,6-diMeO Ph					N
327	4-Ph	H	Bond	4-NO ₂ Ph				0.67 (50% EtOAc/ Hex)	O
328	H	H	Bond	CyBu	---	2.14	217	0.22 (25% EtOAc/ Hex)	G
329	4-CyPen	H	Bond	Ph		3.01	307.3	0.65 (50% EtOAc/ Hex)	N
330	4-Me	Et	Bond	4-Cl Ph		2.94	315	0.65 (50% EtOAc/ Hex)	W
331	4-iPr	H	Bond	4-(trifluoromethoxy)Ph			365.7	0.50 (50% EtOAc/ Hex)	N
332	H	H	O	CyBu		2.17	233	0.56 (50% EtOAc/ Hex)	I
333	4-CyPen	H	Bond	2-Cl Ph		3.16	341.3	0.63 (50% EtOAc/ Hex)	N
334	4-iPr	H	Bond	2H, 3H, 4H-benzo-[b]-1,4 dioxepin-7-yl				0.55 (50% EtOAc/ Hex)	N
335	4-Ph	H	Bond	3-Br Ph		3.46	393	0.79 (50% EtOAc/ Hex)	O
336	4-CyPen	H	Bond	2,4-(dimethyl) Ph		3.27	335.3	0.55 (50% EtOAc/ Hex)	N
337	4-Ph	H	Bond	4-Me-3-pyridyl		1.81	330.1	0.14 (50% EtOAc/ Hex)	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
338	4-Cy Pr	H	Bond	4-(trifluoromethoxy)Ph			363.2	0.60 (50% EtOAc/ Hex)	N
339	4-CyPen	H	Bond	2,5-(dimethoxy) Ph		3.06	367.3	0.55 (50% EtOAc/ Hex)	N
340	4- <i>i</i> Pr	H	NH	3,5-diCl Ph					H
341	4- <i>n</i> -Pr-Amino	H	Bond	4-Cl Ph		2.52	330.3	0.57 (5% MeOH/ EtOAc)	L
342	4- <i>n</i> -Pr	H	Bond	4-Ph Ph		1.37	357.3	0.58 (100% EtOAc)	O
343	4-(2-Methy) Pr Amino	H	Bond	4-Cl Ph		2.62	344.2	0.60 (5% MeOH/ EtOAc)	L
344	4-CyPen	H	Bond	2-Methoxy Ph		3.05	337.3	0.60 (50% EtOAc/ Hex)	N
345	4-Ph	H	Bond	3-Cl Ph		3.4	349	0.72 (50% EtOAc/ Hex)	O
346	4-CyPen	H	Bond	2-naphthyl		3.41	357.3	0.50 (50% EtOAc/ Hex)	N
347	4-Ph	H	Bond	2-F Ph		3.24	333.1	0.77 (50% EtOAc/ Hex)	O
348	4-Me	H	Bond	1, 3, 4-trihydro-quinolin-2-one-6-yl				0.14 (40% EtOAc/ Hex)	N
349	4-Ph	H	Bond	2,4-diCl Ph				0.50 (40% EtOAc/ Hex)	N
350	4- <i>i</i> Pr	Me	Bond	4-Methoxy Ph				0.58 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
351	4-Me	H	Carbonyl	2-furanyl methyl amino				0.25 (3% MeOH/ CH ₂ Cl ₂)	Q
352	4-(4-methyl piperazin-yl Me)	H	Bond	4-CN Ph	3TF A			0.45 (10% 2M NH ₃ in MeOH/ CH ₂ Cl ₂)	S
353	4-CyPen	H	Bond	3-NO ₂ -4-Cl Ph		3.30	386.2	0.53 (50% EtOAc/ Hex)	N
354	4- <i>t</i> -Bu	H	Bond	1-pyrrolidinyl		3.29	364.3	0.85 (100 % EtOAc)	O
355	4-CyPen	H	Bond	2H, 3H, 4H-benzo-[b] 1, 4 dioxepin-7-yl		2.99	379.3	0.55 (50% EtOAc/ Hex)	N
356	4-(2-Methoxyethyl amino)	H	Bond	4-CN Ph				0.375 (10% 2M NH ₃ in MeOH/ CH ₂ Cl ₂)	S
357	4-Ph	H	Bond	2-Pyridyl		2.17	316.1	0.48 (50% EtOAc/ Hex)	O
358	4-Me	H	Carbonyl	4-F-Ph				0.29 (3% MeOH/ CH ₂ Cl ₂)	Q
359	4-Ph	H	Bond	4-(difluoromethoxy) Ph		3.24	381.1	0.72 (50% EtOAc/ Hex)	O
360	4-Me	n-Pr	Bond	4-Cl Ph		3.12	329	0.25 (10% EtOAc/ CH ₂ Cl ₂)	W
361	4-(4-F) Ph	H	Bond	2,4-diCl Ph		3.73	401.3	0.84 (100% EtOAc)	O
362	4-CyPen	H	Bond	3,4-diCl Ph		3.60	375.2	0.58 (50% EtOAc/ Hex)	N
363	4-CyPen	H	Bond	4-(difluoromethoxy) Ph		3.15	373.3	0.60 (50% EtOAc/ Hex)	N

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
364	4-CyPen	H	Bond	3,5-(difluoromethyl) Ph		3.79	443.2	0.55 (50% EtOAc/ Hex)	N
365	4- <i>i</i> Pr	H	Bond		TF A			0.45 (40% EtOAc/ Hex)	N
366	4-(dimethylamino)methyl	H	Bond	4-CN Ph				0.15 (60 EtOAc/ Hex)	S
367	4- <i>i</i> Pr	H	Bond	4-(pyrrolidine) Ph			350.7	0.5 (50% EtOAc/ Hex)	N
368	4-CyPen	Me	Bond	4-Br Ph		3.38	401.2	0.61 (50% EtOAc/ Hex)	N
369	5-Br	H	Bond	3-Pyridyl		2.23	318.2	0.45 (100% EtOAc)	O
370	5-Br	H	Bond	3-F Ph		3.58	366.7	0.92 (100% EtOAc)	O
371	4-(N-pyrrolinomethyl)	H	Bond	4-CN Ph				0.72 (10% 2M NH ₃ in MeOH/ EtOAc)	S
372	4-Ph	H	Bond	4-(trifluoromethyl) Ph		3.51	383.1	0.78 (50% EtOAc/ Hex)	O
373	5-Br	H	Bond	<i>t</i> -Bu		4.06	298.9	0.92 (100% EtOAc)	O
374	4-Et	H	Bond	4-phenyl Ph			343.3	0.50 (50% EtOAc/ Hex)	N
375	4-CyPen	H	Bond	4-(trifluoromethoxy) Ph		3.46	391.3	0.60 (50% EtOAc/ Hex)	N
376	4-Ph	H	Bond	2-Cl Ph		3.27	349	0.69 (50% EtOAc/ Hex)	O
377	4-Ph	H	Bond	4-methoxy Ph				0.50 (40% EtOAc/ Hex)	O
378	5-Br	H	Bond	2,4-dimethyl		3.77	345.1	0.91 (100%	O

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
				Ph				EtOAc)	
379	4-Et	Me	Bond	4- <i>i</i> Bu Ph			337.3	0.50 (50% EtOAc/ Hex)	N
380	5-Br	H	Bond	3-Cl Ph		3.77	353	0.91 (100% EtOAc)	O
381	4-Cy Butyl amino	H	Bond	4-Cl Ph		2.59	342.2	0.56 (5% MeOH/ EtOAc)	L
382	4- CyPen	H	Bond	4-Phenyl Ph			383.4	0.50 (50% EtOAc/ Hex)	N
383	4- <i>i</i> Pr	H	Bond	3,5- (ditrimethyl) Ph		3.61	417.2	0.55 (50% EtOAc/ Hex)	N
384	4- CyPen	Me	Bond	4-methoxy Ph		2.98	351.3	0.58 (50% EtOAc/ Hex)	N
385	4- CyPen	Me	Bond	4-Cl Ph		3.34	355.2	0.63 (50% EtOAc/ Hex)	N
386	4-Me	H	Carbonyl	4-(4-ClPh) Piperazin-1- yl		2.51	399	0.18 (3% MeOH/ CH ₂ Cl ₂)	Q
387	4- CyPen	H	Bond	2,4- dichloroPh		3.56	375.2	0.58 (3% MeOH/ CH ₂ Cl ₂)	N
388	4- <i>i</i> Pr	H	Bond	3-Br Ph			359.7	0.55 (50% EtOAc/ Hex)	N
389	4-Me	H	Bond	Et					G
390	4-Me	H	Bond	4-phenyl Ph				0.33 (40% EtOAc/ Hex)	N
391	4- <i>i</i> Pr	H	Bond	4- trifluoromet hyl Ph		3.24	349.2	0.60 (50% EtOAc/ Hex)	N
392	4-Ph	H	Bond	4-CN Ph		3.03	340.1	0.68 (50% EtOAc/ Hex)	O
393	4-Ph	H	Bond	4-(N- Pyrrolidino Ph)		3.36	384.1	0.43 (50% EtOAc/ Hex)	O

Ex. No.	R ^{21 c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
394	4-Me	H	Carbonyl	(CyHex) amino		2.15	302.2	0.58 (3% MeOH/ CH ₂ Cl ₂)	Q
395	4-Me	H	Carbonyl	4-amino Pyridyl		0.81	297.1	0.17 (3% MeOH/ CH ₂ Cl ₂)	Q
396	4-Me	H	Carbonyl	Ph amino		2.13	296.2	0.34 (3% MeOH/ CH ₂ Cl ₂)	Q
397	4-Me	H	Carbonyl	3-amino Pyridyl				0.17 (3% MeOH/ CH ₂ Cl ₂)	Q
398	4-CyPr	H	Bond	4-phenyl Ph			355.2	0.50 (50% EtOAc/ Hex)	N
399	4-Me	H	Carbonyl	3, 4-di F Ph amino		2.45	332	0.32 (3% MeOH/ CH ₂ Cl ₂)	Q
400	4-Me	H	Carbonyl	1- morpholino		0.83	290.2	0.25 (3% MeOH/ CH ₂ Cl ₂)	Q
401	4-Me	Me	Bond	Me					G
402	4- <i>i</i> Pr	H	Bond	4-phenyl Ph			357.6	0.55 (50% EtOAc/ Hex)	N
403	4- (pipera zin-1- yl)	H	Bond	4-Cl Ph		1.11	357.3	0.10 (5% MeOH/ CH ₂ Cl ₂)	L
404	4-(4- fluorop henyl amino)	H	Bond	4-Cl-Ph		2.63	382.4	0.49 (50% EtOAc/ Hex)	L
405	4- (phenyl amino)	H	Bond	4-Cl Ph		2.62	364.4	0.55 (50% EtOAc/ Hex)	L
406	4-Me	H	Carbonyl	4-(Me Ph amino)		2.37	310.2	0.25 (3% MeOH/ CH ₂ Cl ₂)	Q
407	4-Me	H	Carbonyl	4-(Meo Ph amino)		2.14	326.2	0.25 (3% MeOH/ CH ₂ Cl ₂)	Q
408	4-Me	H	Carbonyl	3-Cl-4-F Ph amino	TF A	2.6	348	0.29 (3% MeOH/ CH ₂ Cl ₂)	Q
409	4-Me	H	Carbonyl	4-(N-(4-CN Ph)		2.19	390	0.25 (3% MeOH/	Q

Ex. No.	R ^{21c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
				piperazin-1-yl				CH ₂ Cl ₂)	
410	4-Me	H	Carbonyl	4-Cl Ph amino		2.52	330	0.38 (3% MeOH/ CH ₂ Cl ₂)	Q
411	4-(1-Imidazolyl methyl)	H	Bond	4-CN Ph				0.60 (10% 2M NH ₃ in MeOH/ EtOAc)	S
412	4-Me	H	Bond	4-(amidine) Ph		1.82	295	0.10 (20% NH ₃ in EtOH/ 80% CH ₂ Cl ₂)	O
413	4-nPr	4-Me Ph	Bond	4-Cl Ph		1.45	405.3	0.83 (100% EtOAc)	O
414	4-CyPr	H	Bond	3-CN Ph			304.2	0.55 (50% EtOAc/ Hex)	N
415	4-Me	H	Bond	4-Pyridyl				0.31 (3% MeOH/ CH ₂ Cl ₂)	O
416	4-Me	H	Carbonyl	3-CN Ph amino	TF A	2.22	321	0.25 (3% MeOH/ CH ₂ Cl ₂)	Q
417	4-CyPr	H	Bond	3-(3,4-diCl-Ph) Isoxazol-5-yl				0.20 (40% EtOAc/ Hex)	O
418	4-t-Bu	Me	Bond	4-i-Bu		3.69	365.3	0.79 (100% EtOAc)	O
419	4-(4-i Pr piperazin-1-yl methyl)	H	Bond	4-CN Ph	3TF A			0.32 (10% 2M NH ₃ in MeOH/ CH ₂ Cl ₂)	S
420	4-(di Me Amino Ethyl Amino)	H	Bond	4-CN Ph				0.13 (10% 2M NH ₃ in MeOH/ CH ₂ Cl ₂)	S

Ex. No.	R ^{21 c}	J	L ¹	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f d(Solvent)	General Method
	me thyl)								
421	4-(Me amino me thyl)	H	Bond	4-CN Ph				0.25 (10% 2M NH ₃ in MeOH/CH ₂ Cl ₂)	S
422	4-(Et amino me thyl)	H	Bond	4-CN Ph				0.30 (10% 2M NH ₃ in MeOH/CH ₂ Cl ₂)	S
423	4-(iPr amino) Me	H	Bond	4-CN Ph				0.35 (10% 2M NH ₃ in MeOH/CH ₂ Cl ₂)	S

Note^a - HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

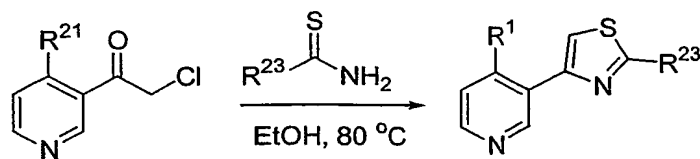
Note^b - Molecular ion data obtained via electrospray ionization.

Note^c -The following abbreviations were used; Ac-acetyl, Cl-chloro, CF₃-trifluoromethyl, CN-cyano, COOH-carboxylic acid, COOEt-ethyl ester, CyPen-cyclopentyl, CyPr-cyclopropyl, diCl-dichloro, diCF₃ -ditrifluoromethyl, diF-difluoro, Et-ethyl, F-fluoro, iBu- isobutyl, iPr- isopropyl, Me-methyl, MeO-methoxy, n-Bu-n-butyl NMe₂-dimethylamine, NO₂-nitro, Ph-phenyl, Pr-propyl, t-Bu-t-butyl

Note^d - The following abbreviation was used: Hex – hexanes

Note^e - NMR spectra data was in agreement with the assigned structure

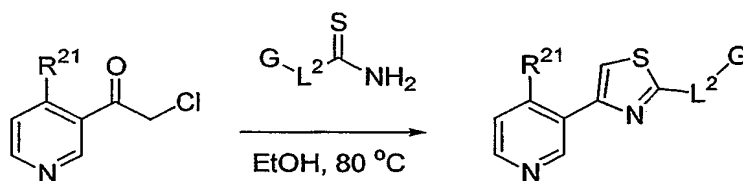
General Method T: Synthesis of 4-(3-Pyridyl)-Thiazoles by Parallel Methods



In a 7 mL brown vial were placed the chloroketone (1.0 mmol) and the thioamide (1 eq, 1

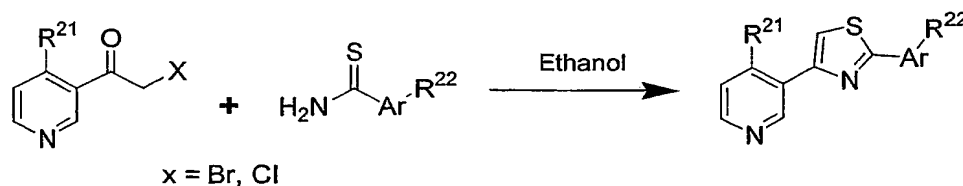
mmol) in 3 mL of absolute EtOH. The vial was capped under Ar and shaken at 80 °C overnight. Upon cooling, in several examples the desired product crystallized out of solution and was simply removed by filtration. In other cases, where no crystalization occurred, or where impurities remained, the EtOH was removed and the desired solid heated in a minimal amount of CH₃CN and filtered to yield the pure product. Yields for this reaction were typically 60-90% of the HCl salt. Several examples were then suspended in saturated NaHCO₃ and extracted with CH₂Cl₂ to provide the free base.

General Method U: Synthesis of 4-(3-Pyridyl)-2-aminothiazoles by Parallel Methods



In a 7 mL brown vial were placed the chloroketone (1.0 mmol) and the thiourea (1 equiv., 1 mmol) in 3 mL of absolute EtOH. The vial was capped under Ar and shaken at 80 °C overnight. Upon cooling, in several examples the desired product crystallized out of solution and was simply removed by filtration. In other cases, where no crystalization occurred, or where impurities remained, the EtOH was removed and the desired solid heated in a minimal amount of CH₃CN and filtered to yield the pure product. Yields for this reaction were typically 60-90% of the HCl salt. Several examples were then suspended in saturated NaHCO₃ and extracted with CH₂Cl₂ to provide the free base.

General Method V: Synthesis of 4-(3-Pyridyl)-Thiazoles by Parallel Methods

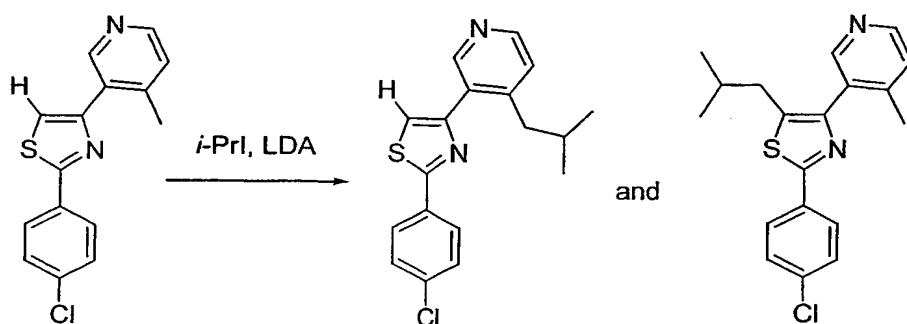


An EPA vial was charged the thioamide (11.2 mmol) and the α -halo ketone (13.5 mmol, 1.20 eq.). To this was added 15 mL of anhydrous ethanol. In the event that the α -halo ketone was a salt, then pyridine (1.2 eq.) was also added to the vial. The vial was capped tightly and shaken in a heating block overnight at 82 °C. The reaction mixture was concentrated down and taken up in 2 mL of dichloromethane and 2 mL of water. It was basified with triethylamine (~10 drops) and extracted twice with dichloromethane. The

organic layers were combined and concentrated to dryness, and the crude residue was dissolved in hot DMSO. The compound was purified by Gilson HPLC to yield the desired thiazole derivative.

Example 424

- 5 **General Method W: Alkylation of 4-Methyl Pyridine Containing Thiazoles, as Exemplified by the Preparation of 4-(4-(2-methyl-1-propyl)-3-pyridyl)-2-(4-chlorophenyl) thiazole and 4-(4-methyl-3-pyridyl)-5-(2-methyl-1-propyl)-2-(4-chlorophenyl) thiazole**

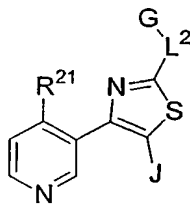


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- To a solution of LDA 1.05 mmol) in THF, at -78°C , was added the 4-methyl pyridine-containing thiazole (0.70 mmol) followed by the isopropyl iodide. The mixture stirred at -78°C for 1 h, at 0°C for 1 h, then at rt for 2 h. MeOH was then added to the reaction and the mixture was evaporated to dryness. The residue was purified by silica gel chromatography to afford the alkylated pyridine-containing thiazoles (0.062 mmol). NMR and MS are consistent with the assigned structures.

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Table III. 4-(3-Pyridyl)thiazoles



20

Ex. No.	R ²¹ c	J	L ²	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
587	4-Me	H	NH	2-Me-5-F Ph	HCl	2.08	300.3		U
587	4-Me	H	NH	Ph		1.86	268.2		U
587	4-Me	H	Bond	2-F Ph		1.91	271.2		T

Ex. No.	R ^{21 c}	J	L ²	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
587	4-Me	H	NH	2-CF ₃ Ph	HCl	2.06	336.2		U
587	4-Me	H	NH	4-F Ph	HCl	1.91	286.3 [M+2] ⁺		U
587	4-Me	H	Bond	4-Me Ph	HCl	2.16	267.3		T
587	4-Me	H	Bond	2-MeO Ph	HCl	2.01	282.9		T
587	4-Me	H	NH	3-F Ph	HCl	1.96	286.2		U
587	4-Me	H	Bond	3-F Ph	HCl	2.00	271.3		T
587	4-Me	H	NH	2-F Ph		1.90	286.2		U
587	4-Me	H	Bond	3-NO ₂ Ph	HCl	2.00	298.2		T
587	4-Me	H	Bond	3-CF ₃ Ph	HCl	2.36	321.2		T
587	4-Me	H	Bond	5-NO ₂ thien-2-yl	HCl	2.48	324.2	0.70 (4% 2M NH ₃ - MeOH/ CH ₂ Cl ₂)	V
587	4-Me	H	NH	4-Me Ph	HCl	2.70	282.3		U
587	4-Me	H	NH	2,4-diF Ph	HCl	1.96	304.3		U
587	4-Me	H	NH	4-F Ph		1.94	286.2		U
587	4-Me	H	Bond	3-MeO Ph	HCl	2.00	283.3		T
587	4-Me	H	Bond	4-[(4,5- diCl-1H- imidazol-1- yl)Me]Ph	HCl	2.18	401.1[M] ⁺		T
587	4-Me	H	NH	2-Cl Ph	HCl	2.02	302.2		U
587	4-Me	H	NH	Ph	HCl	2.38	268.3		U
587	4-Me	H	NH	2-MeO-4- Cl Ph	HCl	2.14	332.2		U
587	4-Me	H	NHCH ₂ C H ₂	Ph		1.99	296.3		U
587	4-Me	H	NH	N-n-Bu	TFA	1.54	248.2		U
587	4-Me	H	Bond	4-Me Pyrid-3-yl	2 HCl	0.77	268.2	0.40 (4% 2M-NH ₃ - MeOH/ CH ₂ Cl ₂)	V
587	4-Me	H	NH	3-MeO Ph	HCl	1.90	298.2		U
587	4-Me	H	NH	2-F Ph	HCl	1.83	286.2		U
587	4-Me	H	Bond	2,3- dihydro-1- benzofuran -5-yl	HCl	2.01	295.3		T
587	4-Me	H	Bond	2-Cl Ph	HCl	2.15	287.1		T
587	4-Me	H	Bond	2-MeO Ph		2.06	283.2		T
587	4-Me	H	Bond	4-MeO Ph	HCl	1.92	283.3		T
587	4-Me	H	NH	3-Cl Ph	HCl	2.16	302.2		U
587	4-Me	H	Bond	3-Cl Ph	HCl	2.22	287.1		T
587	4-Me	H	Bond	2-NO ₂ Ph	HCl	1.80	298.2		T
587	4-Me	H	NH	2-MeO Ph	HCl	1.96	286.2		U
587	4-Me	H	NH	4-Cl Ph	HCl	2.14	302.2		U

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H) ⁺	TLC R _f (Solvent) ^d	General Method ^e
							[M+2] ⁺		
587	4-Me	H	NH	pyridin-3-yl	HCl	0.72	269.3		U
587	4-Pr	H	Bond	thien-2-yl		2.2	287.3	0.68 (EtOAc)	V
587	4-Me	H	NH	N-benzyl		1.85	282.2		U
587	4-Me	H	NH	3-CN Ph	HCl	1.86	293.3		U
587	4-Me	H	Bond	2,3-diCl Ph	HCl	2.40	321.3		T
587	4-Me	H	Bond	naphth-2-yl	HCl				T
587	4-Pr	H	Bond	5-NO ₂ thien-3-yl		2.31	332.3	0.61 (EtOAc)	V
587	4-Me	H	Bond	3-F-4-Me Ph	HCl	2.25	285.3		T
587	4-Me	H	Bond	4-Cl Ph	HCl	2.22	287.2	0.50 (4% 2M NH ₃ - MeOH/ CH ₂ Cl ₂)	V
587	4-Me	H	Bond	4-NO ₂	HCl	2.04	298.2		T
587	4-Pr	H	Bond	6-CF ₃ pyridin-3-yl		1.75	283.3	0.22 (EtOAc)	V
587	4-Me	H	Bond	naphth-2-yl		2.34	303.2		T
587	4-Me	H	NH	cyclohexyl		1.86	274.2		U
587	4-Me	H	NHCH ₂	2-furyl	TFA	0.66	272.2		U
587	4-Me	H	Bond	3-CN Ph	TFA			0.34 (50% EtOAc/H ex)	V
587	4-Pr	H	Bond	3-NO ₂ Ph		2.35	326.3	0.6 (EtOAc)	V
587	4-Me	H	NH	2,4-diCl Ph	HCl	2.30	336.2[M] J ⁺		U
587	4-Me	H	Bond	3-Cl-4-F Ph	HCl	2.30	305.3		T
587	4-Me	H	Nme	Ph	HCl	1.99	282.3		U
587	4-Me	H	Bond	6-Me pyridin-3-yl	2HCl			0.50 (4% 2MNH ₃ - MeOH/ CH ₂ Cl ₂)	V
587	4-Me	H	NH	2,5-diMeO Ph	HCl	1.97	328.2		U
587	4-Me	H	Bond	2-F Ph	HCl	2.00	271.3		T
587	4-Me	H	Nme	Ph		2.02	282.2		U
587	4-Pr	H	Bond	Ph		2.28	281.3	0.68 (EtOAc)	V
587	4-Pr	H	Bond	pyrid-3-yl				0.45 (EtOAc)	V
587	4-Pr	H	Bond	thien-3-yl		2.16	287.3	0.66 (EtOAc)	V

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
587	4-Me	H	NH	N-[3-(Me sulfanyl)Ph]	HCl	2.16	314.2		U
587	4-Me	H	Bond	4-CF ₃ Ph	HCl	2.40	321.7		T
587	4-Me	H	Bond	2,4-diCl Ph	HCl	2.40	321.7		T
587	4-Me	H	Bond	thien-2-yl				0.49 (5% MeOH/ CH ₂ Cl ₂)	V
587	4-Me	H	NH	N-4-Me benzyl		2.06	296.2		U
587	4-Pr	H	Bond	Pyrid-4-yl		0.91	282.3	0.21 (EtOAc)	V
587	4-Me	H	NH	3,5-diCl Ph	HCl	3.06	336.3		U
587	4-Pr	H	Bond	4-CN Ph		2.23	306.4	0.64 (EtOAc)	V
587	4-Pr	H	Bond	4-NO ₂ Ph		2.36	326.3	0.62 (EtOAc)	V
587	4-Pr	H	Bond	4-Cl Ph		2.55	315.5	0.65 (EtOAc)	V
587	4-Me	H	Bond	4-CF ₃ Ph		2.33	321.2		T
587	4-Me	H	NH	3-CF ₃ Ph	HCl	2.26	336.3		U
587	4-Me	H	NH	pyrid-3-yl		0.68	269.2		U
587	4-Me	H	Bond	3-NO ₂ -4-MeO Ph	HCl	2.06	328.1		T
587	4-Me	H	NH	4-CF ₃ Ph	HCl	2.28	336.3		U
587	4-Me	H	Bond	4-CN Ph	HCl	1.85	278.2		T
587	4-Me	H	NH	4-Cl Ph		1.91	302.2		U
587	4-Me	H	CH ₂ O	2-Cl Ph	TFA	2.19	317.2		T
587	4-Me	H	NH	N-benzhydryl		2.36	358.2		U
587	4-Me	H	Bond	3,5-diCF ₃ Ph	HCl	2.65	389.2		T
587	4-Me	H	Bond	4-CN Ph		1.85	278.2		T
587	4-Me	H	NH	4-MeO Ph	HCl	1.83	298.2		U
587	4-Me	H	Bond	4-CN Ph	MSA		[M+2] ⁺		V
587	4-Pr	H	Bond	2-pyrazine		1.75	283.3	0.55 (EtOAc)	V
587	4-Me	H	NH	N-4-Cl benzyl		2.12	316.2		U
587	4-Me	Cl	Bond	4-Cl Ph				0.20 (33% EtOAc/H ex)	V
587	4-Me	H	NHCH ₂	2-tetrahydrofuran-2-yl	TFA	0.64	276.2		U

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
587	4-IsoBu	H	Bond	4-Cl Ph				0.21 (33% EtOAc/Hex)	W
587	4-Me	H	NH	2,4-diMeO Ph	HCl	1.95	328.2		U
587	4-Me	H	NH	4-diMeN Ph	HCl	0.18	311.3		U
587	4-Me	H	NH	4-CN Ph	HCl	2.35	293.3		U
587	4-Me	H	Bond	2-Pyrazine				0.38 (5% 2N NH ₃ MeOH/C H ₂ Cl ₂)	V
587	4-Me	H	NH	4-MeO Ph		1.85	298.2		U
587	4-Me	H	Bond	4-(1,2,3-thiadiazol-4-yl)Ph	HCl	2.03	337.1		T
587	4-Me	H	Bond	isoxazol-5-yl	HCl	0.96	244.1		T
587	4-Me	H	NHCH ₂ C H ₂	N-piperdiny		0.64	303.2		U
587	4-Me	H	CH ₂ O	4-Cl Ph	HCl	2.26	317.1		T
587	4-Me	H	NHCH ₂ C H ₂	N-morpholino	2 TFA	0.65	305.1		U
587	4-Me	H	NHCH ₂	4-MeO Ph		1.92	312.2		U
587	4-Me	H	Bond	4-t-Bu Ph		2.59	309.4		T
587	4-Me	H	NHCH ₂ C H ₂ CH ₂	NMe ₂	2 TFA	0.65	277.2		U
587	4-Me	H	NH	4-Ac Ph	HCl	1.79	310.3		U
587	4-Me	H	NH	3-CO ₂ Et Ph	HCl	2.15	340.2		U
587	4-Me	H	NH	4-NO ₂ Ph	HCl	1.96	313.2		U
587	4-Me	H	NH	4-CO ₂ Et Ph	HCl	2.14	340.2		U
587	4-Me	H	NHCH ₂ C H ₂ CH ₂	N-morpholine		0.66	319.2		U
587	4-Me	H	Bond	2,6-diCl-4-CF ₃ Ph	HCl	2.52	389.2		T
587	4-Me	H	Bond	Benzene-4-carboximidamide		0.85	295	0.01 (15% 2M NH ₃ /EtOAc)	V
587	4-Me	H	Bond	1,1'-biphenyl	HCl	2.54	329.3		T
587	4-Pr	Et	Bond	4-Cl Ph				0.36 (20% EtOAc/Hex)	W
587	4-Me	H	NH	4-(Benzyloxy)Ph	HCl	2.43	374.2		U
587	4-Me	H	NH	4-COOH	TFA	1.51	312.3		U

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
				Ph					
587	4-Me	H	Bond	4-(5-CF ₃ - 2-pyridi nyl-2-oxy) Ph	2 TFA	2.53	414.3		T
587	4-Me	H	NH ₂	-----	HCl				U
587	4-Me	H	Bond	2,4-diCl Ph		2.41	321.2[M I ⁺		T
587	4-Me	H	Bond	4-COOH Ph	HCl	2.59			V
587	4-CF ₃	H	Bond	4-CN Ph		3.08			V
587	4- <i>i</i> Pr	H	Bond	1- isoquinolin e	TFA			0.1571 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	2,6-diCl-4- pyridine	TFA			0.1440 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	3-Cl Ph	TFA			0.18 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	3-Cl Ph	TFA			0.17 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	3-Cl-Ph	TFA			0.17 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	Ph	TFA			0.16 (20% EtOAc/ Hex)	R
587	4- <i>i</i> Pr	H	Bond	Ph	TFA			0.20 (20% EtOAc/ Hex)	R
587	4-Et	H	Bond	4-Cl Ph	TFA			0.16 (20% EtOAc/ Hex)	R
587	4- <i>i</i> Pr	H	Bond	4-Cl Ph	TFA			0.16 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	3-NO ₂ Ph	TFA			0.10 (20% EtOAc/	V

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
								Hex)	
587	4-CyPr	H	Bond	4-Cl Ph	TFA			0.14 (20% EtOAc/ Hex)	V
587	4-CyPr	H	Bond	3-NO ₂ Ph	TFA			0.08 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	3-NO ₂ Ph	TFA			0.10 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	3-CN Ph	TFA			0.07 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	3-CN Ph	TFA			0.03 (20% EtOAc/ Hex)	V
587	4-CyPr	H	Bond	3-CN Ph	TFA			0.03 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	4-NO ₂ Ph	TFA			0.05 (20% EtOAc/ Hex)	V
587	4-CyPr	H	Bond	4-NO ₂ Ph	TFA			0.04 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	4-NO ₂ Ph	TFA			0.06 (20% EtOAc/ Hex)	V
587	4-CyPr	H	Bond	3-(6-Me pyridin-2- ol)	TFA			0.0 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	3-(6-Me pyridin-2- ol)	TFA			0.0 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	2-Me pyridin-5- yl	TFA			0.05 (20% EtOAc/ Hex)	V
587	4-CyPr	H	Bond	2-Me pyridin-5-	TFA			0.038 (20%	V

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a, b} min	MS ^{a, b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
				yl				EtOAc/ Hex)	
587	4- <i>i</i> Pr	H	Bond	2-Me pyridin-5- yl	TFA			0.04 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	4-Me Ph	TFA			0.09 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	4-Me Ph	TFA			0.11 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	4-MeO Ph	TFA			0.06 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	4-MeO Ph	TFA			0.08 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	4-CF ₃ Ph	TFA			0.09 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	4-CF ₃ Ph	TFA			0.08 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	4-CF ₃ Ph	TFA			0.09 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	2-MeO pyridin-5- yl	TFA			0.07 (20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	2-MeO pyridin-5- yl	TFA			0.09 (20% EtOAc/ Hex)	V
587	4-Et	H	Bond	3,4-diCl Ph	TFA			0.09 (20% EtOAc/ Hex)	V
587	4- CyPr	H	Bond	3,4-diCl Ph	TFA			0.07(20% EtOAc/ Hex)	V
587	4- <i>i</i> Pr	H	Bond	3,4-diCl Ph	TFA			0.07	V

Ex. No.	R ^{21c}	J	L ²	G ^c	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^d	General Method ^e
								(20% EtOAc/Hex)	
587	4-Et	H	Bond	4-CN Ph	TFA			0.04 (20% EtOAc/Hex)	V
587	4-CyPr	H	Bond	4-CN Ph	TFA			0.034 (20% EtOAc/Hex)	V
587	4- <i>i</i> Pr	H	Bond	4-CN Ph	TFA			0.05 (20% EtOAc/Hex)	V
587	4-Me	H	Bond	5-Br pyridin-3-yl				0.31 (100% EtOAc)	V
587	4-Me	H	Bond	4-pyridinyl				0.35 (5% 2N NH ₃ MeOH/C H ₂ Cl ₂)	V

Note^a HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA.

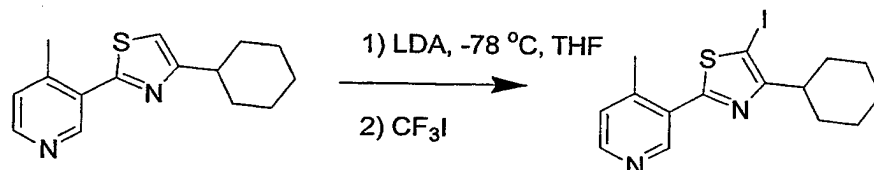
Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Note^b - Molecular ion data obtained via electrospray ionization.

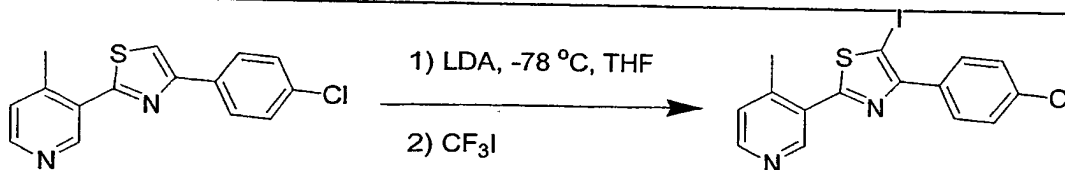
Note^c - The following abbreviations were used; Ac-acetyl, Cl-chloro, CF₃-trifluoromethyl, CN-cyano, COOH-carboxylic acid, COOEt-ethyl ester, CyPr-cyclopropyl, DiCl-dichloro, diCF₃ -ditrifluoromethyl, diF-difluoro, Et-ethyl, F-fluoro, *i*Pr- isopropyl, Me-methyl, MeO-methoxy, n-Bu-n-butyl NMe₂-dimethylamine, NO₂-nitro, Ph-phenyl, Pr-propyl, t-Bu-t-butyl

Note^d - The following abbreviation was used: Hex – hexanes

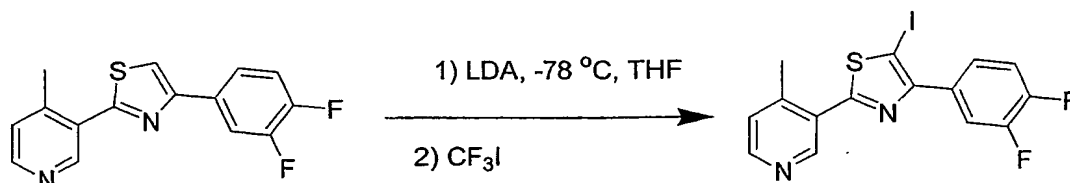
Note^e - NMR spectra data was in agreement with the assigned structure

Example 584**General Method X, as Exemplified by the Preparation of 3-(4-cyclohexyl-5-iodo-1,3-thiazol-2-yl)-4-methylpyridine**

To a solution of LDA (0.581 mmol) in dry THF (5 mL) at -78°C was added 3-(4-cyclohexyl-1,3-thiazol-2-yl)-4-methylpyridine (100 mg, 0.387 mmol) as a solution in dry THF (2 mL) over 10 min. The red solution was stirred at -78°C for 30 min. Excess CF_3I gas was condensed in the reaction with a fritted bubbler slowly until the reaction turns clear. The reaction was stirred at -78°C for 5 min, then warmed up to -25°C and stirred for 25 min. The reaction was then allowed to warm to rt over 1 h with the ice bath removed. The reaction mixture was concentrated *in vacuo* and the crude orange oil purified directly by silica gel chromatography (EtOAc/hexanes). The product was isolated as a yellow solid in 68% yield (86 mg, 0.263 mmol): TLC R_f 0.54 (50% EtOAc/hexanes); LCMS $(\text{M}+\text{H})^+$ 385 t_R = 3.26 min. ^1H NMR ($\text{DMSO}-d_6$) 8.81 (s, 1H), 8.48 (d, 1H, $J = 5$ Hz), 7.39 (d, 1H, $J = 5$ Hz), 2.80 (m, 1H), 2.52 (s, 3H), 1.74 (m, 5H), 1.58 (m, 2 H), 1.2-1.42 (m, 3H).

Example 585**Preparation of 3-[4-(4-Chlorophenyl)-5-iodo-1,3-thiazol-2-yl]-4-methylpyridine**

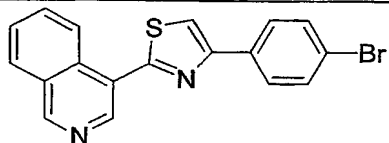
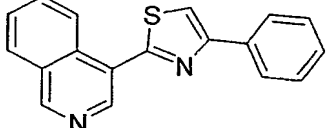
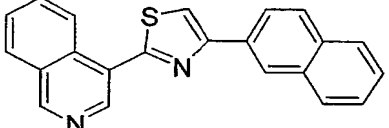
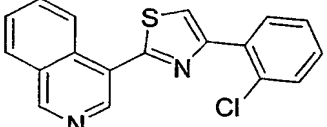
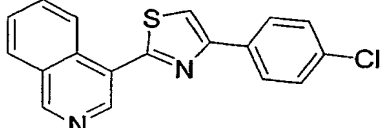
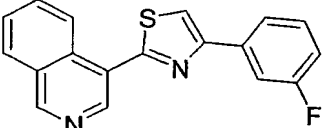
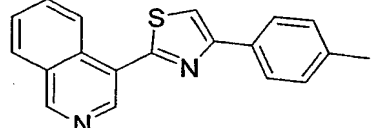
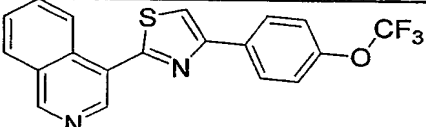
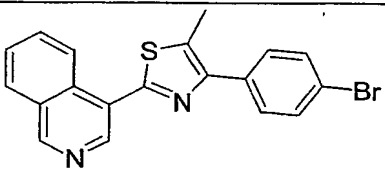
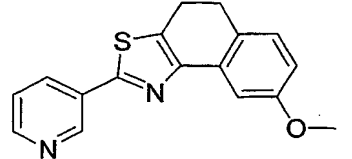
3-[4-(4-chlorophenyl)-5-iodo-1,3-thiazol-2-yl]-4-methylpyridine was prepared from 3-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]-4-methylpyridine according to General Method X: TLC R_f 0.50 (50% EtOAc/hexanes); LCMS $(\text{M}+\text{H})^+$ = 413, t_R = 3.23 min.

Example 586**Preparation of 3-[4-(3,4-Difluorophenyl)-5-iodo-1,3-thiazol-2-yl]-4-methylpyridine**

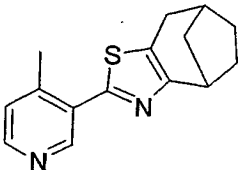
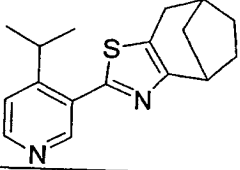
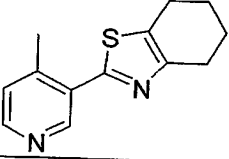
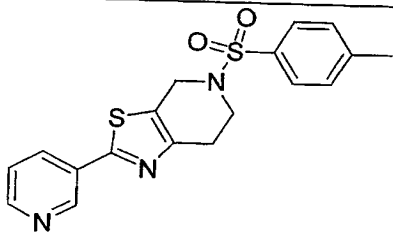
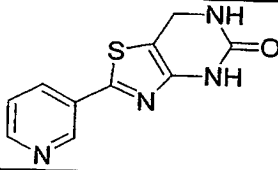
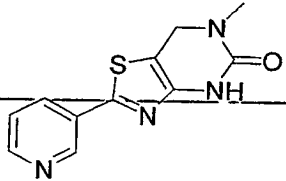
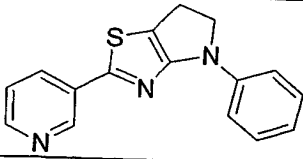
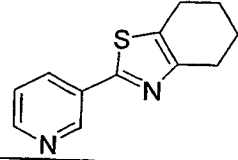
3-[4-(3,4-difluorophenyl)-5-iodo-1,3-thiazol-2-yl]-4-methylpyridine (BAY 65-6863) was prepared from 3-[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]-4-methylpyridine according to General Method X: TLC R_f 0.54 (50% EtOAc/hexanes); LCMS 415 ($M+H^+$), t_R = 3.10 min.

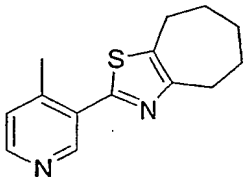
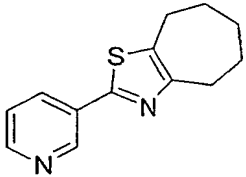
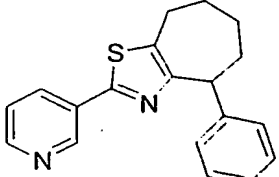
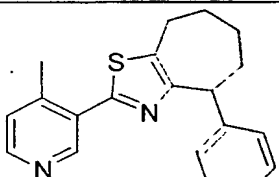
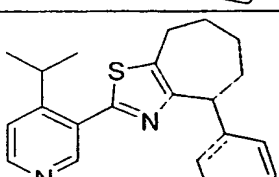
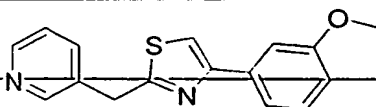
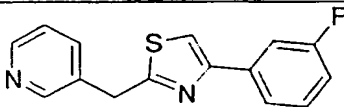
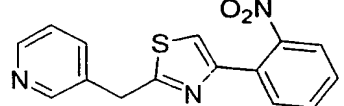
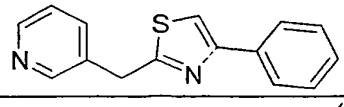
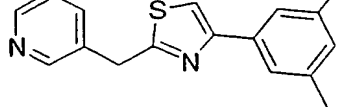
Table IV-Other Thiazoles

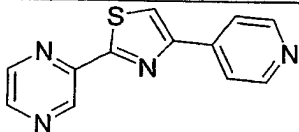
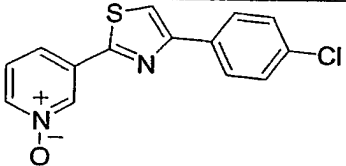
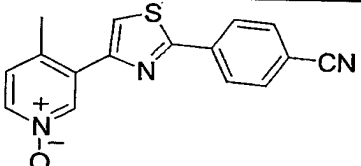
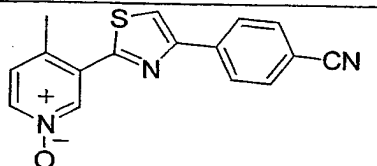
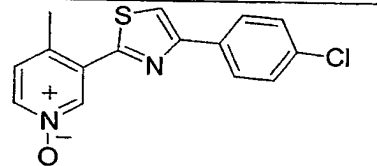
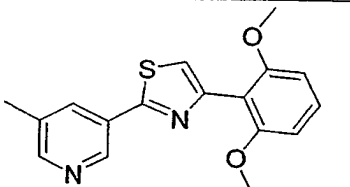
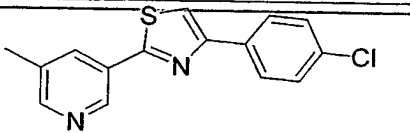
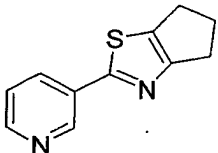
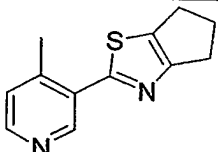
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587				334.2	0.55 (50% EtOAc/hex)	N
588				368.2	0.50 (50% EtOAc/hex)	N
589				367.3	0.55 (50% EtOAc/hex)	N
590				334.2	0.50 (50% EtOAc/hex)	N
591				357.3	0.55 (50% EtOAc/hex)	N
592				307.3	0.60 (50% EtOAc/hex)	N

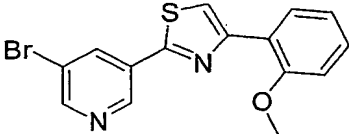
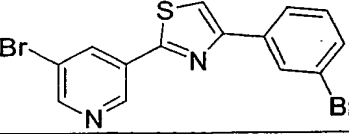
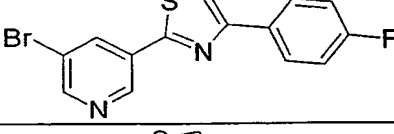
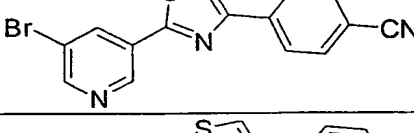
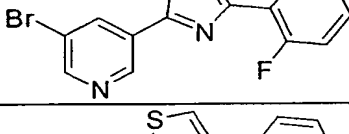
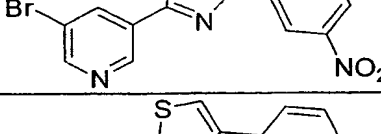
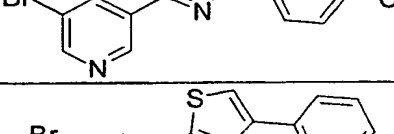
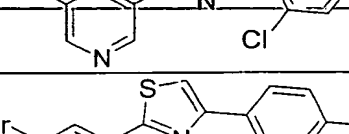
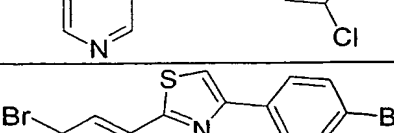
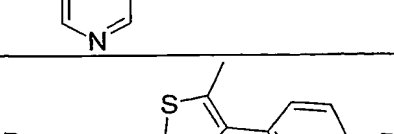
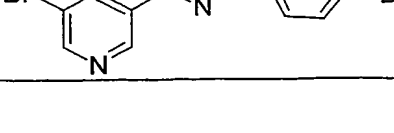
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593				367.2	0.55 (50% EtOAc/hex)	N
594				289.3	0.55 (50% EtOAc/hex)	N
595				337.3	0.50 (50% EtOAc/hex)	N
596				323.3	0.55 (50% EtOAc/hex)	N
597				323.3	0.60 (40% EtOAc/hex)	N
598				307.3	0.60 (50% EtOAc/hex)	N
599				303.3	0.50 (50% EtOAc/hex)	N
600						O
601						O
602				295	0.27 (25% EtOAc/hex)	M

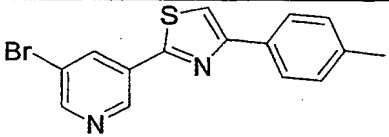
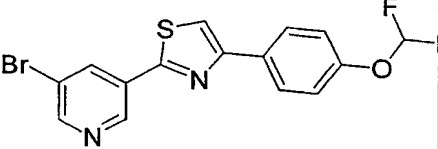
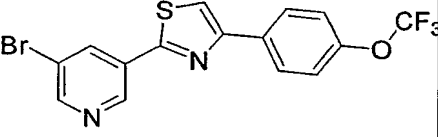
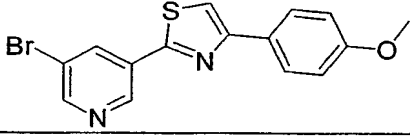
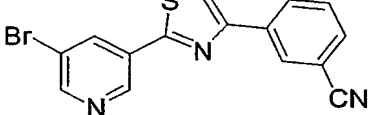
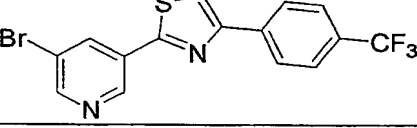
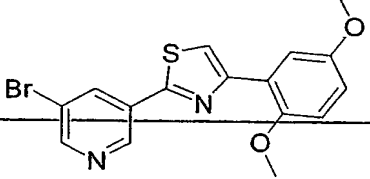
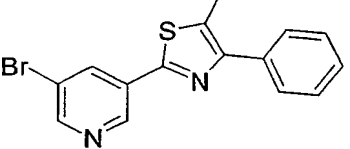
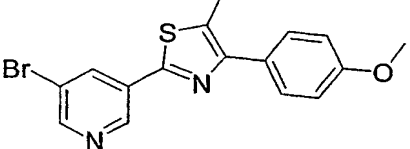
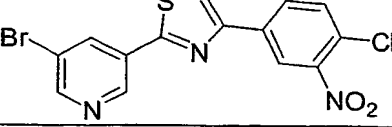
Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
603			3.68	347	0.63 (50% EtOAc/hex)	G
604			2.49	279.2	0.32 (40% EtOAc/hex)	O
605			2.73	295	0.37 (25% EtOAc/hex)	N
606			1.91	257	0.38 (100% EtOAc)	G
607			1.65	271	0.42 (100% EtOAc)	G
608			3.38	313	0.48 (50% EtOAc/hex)	G
609			2.29	263	0.50 50% EtOAc/hex)	G
610			2.81	265	0.45 (25% EtOAc/hex)	M
611			2.31	243	0.38 (50% EtOAc/hex)	G

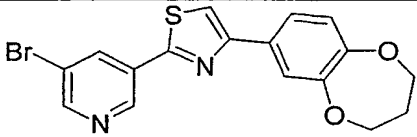
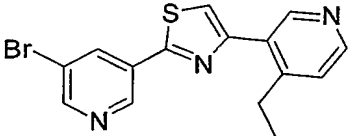
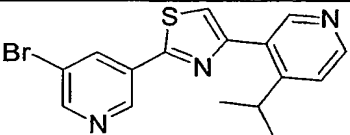
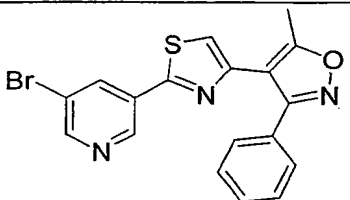
Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
612			2.10	257	0.33 (50% EtOAc/hex)	G
613			2.63	285	0.50 (50% EtOAc/hex)	G
614			1.80	231	0.55 (50% EtOAc/hex)	G
615			2.44	372	0.43 (100% EtOAc)	G
616			0.64	233	0.25 (10% MeOH/EtO Ac)	G
617			0.80	247	0.46 (10% MeOH/EtO Ac)	G
618			2.80	280	0.40 (33% EtOAc/hex)	G
619			2.02	217	0.20 (50% EtOAc/hex)	G

Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
620			217	245	0.29 (50% EtOAc/hex)	G
621			2.36	231	0.47 (50% EtOAc/hex)	G
622			2.93	307	0.60 (50% EtOAc/hex)	G
623			2.64	321	0.63 (50% EtOAc/hex)	G
624			2.98	349	0.53 (50% EtOAc/hex)	G
625					0.08 (50% EtOAc/hex)	O
626					0.10 (50% EtOAc/hex)	O
627					0.05 (50% EtOAc/hex)	O
628					0.09 (50% EtOAc/hex)	O
629					0.09 (50% EtOAc/hex)	O

Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
630		TFA			0.27 (3% MeOH/CH ₂ Cl ₂)	O
631					0.43 (6% MeOH/CH ₂ Cl ₂)	R
632			2.89	294.33	0.11 (10% MeOH/EtOAc)	R
633			3.18	294.33	0.13 (10% MeOH/EtOAc)	R
634			2.54	289.2	0.43 (6% MeOH/CH ₂ Cl ₂)	R
635				313		N
636					0.60 (50% EtOAc/hex)	N
637			1.76	203	0.67 (EtOAc)	G
638			1.51	217	0.56 (EtOAc)	G

Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
639					0.91 (EtOAc)	O
640					0.91 (EtOAc)	O
641					0.91 (EtOAc)	O
642					0.86 (EtOAc)	O
643					0.92 (EtOAc)	O
644					0.87 (EtOAc)	O
645					0.92 (EtOAc)	O
646					0.93 (EtOAc)	O
647					0.88 (EtOAc)	O
648					0.91 (EtOAc)	O
649					0.90 (EtOAc)	O

Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
650					0.91 (EtOAc)	O
651					0.91 (EtOAc)	O
652					0.91 (EtOAc)	O
653					0.90 (EtOAc)	O
654					0.87 (EtOAc)	O
655					0.92 (EtOAc)	O
656					0.90 (EtOAc)	O
657					0.90 (EtOAc)	O
658					0.90 (EtOAc)	O
659					0.85 (EtOAc)	O

Ex. No.	Structure ^d	Salt	t _R ^{a,b} min	MS ^{a,b} (M+H ⁺)	TLC R _f (Solvent) ^c	General Method
660					0.88 (EtOAc)	O
661		TFA			0.14 (20% EtOAc/hex)	O
662		TFA			0.15 (20% EtOAc/hex)	O
663		TFA			0.25 (20% EtOAc/hex)	O

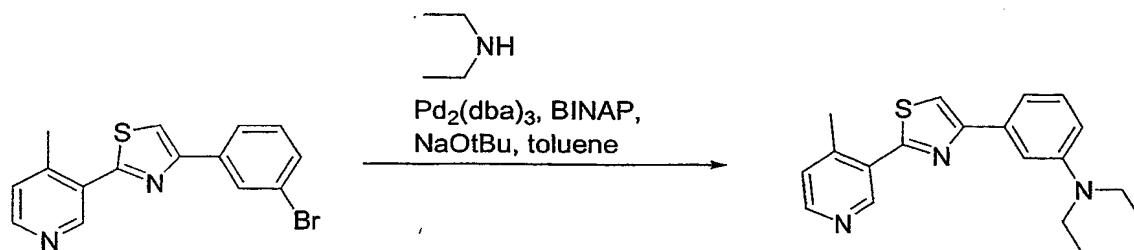
Note^a- HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Note^b- Molecular ion data obtained via electrospray ionization.

Note^c- The following abbreviation was used: Hex – hexanes

Note^d- NMR spectra data was in agreement with the assigned structure

General Method Y, as Exemplified by the Preparation of 2-(4-Methyl-3-pyridyl)-4-(3-(diethylamino)phenyl)thiazole



To a solution of 2-(4-methyl-3-pyridyl)-4-(3-bromophenyl)thiazole (0.06 mmol) in toluene (5 mL) was added diethyl amine (0.25 mmol), NaOtBu (0.09 mmol), BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (0.0054 mmol), Pd₂(dba)₃ (0.0018 mmol) under argon. The mixture was heated to reflux for 24 h. EtOAc and H₂O were added and the organic and aqueous phase was separated. The organic phase was dried over MgSO₄, filtered and evaporated to dryness. The mixture was purified by Gilson HPLC to afford 4 mg (25%) of the title compound: TLC R_f 0.65 (100% EtOAc). The ¹H NMR and MS were consistent with the assigned structure

Determination of the activity of the compounds of the invention

C17,20 Lyase inhibitory activity of compounds can be determined using, e.g., the biochemical or the cellular assays set forth in the Examples. A person of skill in the art will recognize that variants of these assays can also be used.

~~The compounds of the invention can also be tested in animal models, e.g., animal~~
models of prostate or breast cancer.

Each of the compounds of the invention was subjected to a biochemical assay and a cellular assay for determining its C17,20 lyase inhibitory activity.

Human and murine C17,20 lyase biochemical assays:

Recombinant human C17,20 lyase (hLyase) was expressed in (Sf9) cells, and hLyase enriched microsomes were prepared from cultures as described in the following reference: Baculovirus Expression of Bovine P₄₅₀ in Sf9 Cells and Comparison with Expression in Yeast, Mammalian Cells, and *E. Coli*. Barnes H. J.; Jenkins, C. M.; Waterman, M. R., *Archives of Biochemistry and Biophysics* (1994) 315(2) 489-494. Recombinant murine

C17,20 lyase (mLyase) was prepared in a similar manner. hLyase and mLyase preparations were titrated using assay conditions to determine protein concentrations to be used for assays. Both mLyase and hLyase assays were run in an identical manner except that cytochrome b5 was omitted in the murine assays.

5 Test compounds were diluted 1:4, serially in six steps, with 100% DMSO starting from 800 μ M going to 51.2 nM reserving the first 2 columns for the generation of a standard curve. Each of these compound solutions in 100% DMSO was further diluted twenty fold in H₂O to obtain compound concentrations ranging from 40 μ M to 2.56 nM in 5% DMSO. Dehydroepiandrosterone (DHEA) standards were serially diluted in 100% DMSO from 400
10 μ M down to 120 nM in half-log dilutions. Each dilution was further diluted twenty fold in H₂O to obtain 20 μ M to 6 nM solutions in 5% DMSO using the first 2 columns. Five μ L of these 5% DMSO dilutions were used in the assay.

Clear-bottomed opaque 96 well assay plates were loaded with 50 μ L of assay buffer (50 mM Na₃PO₄, pH 7.5) and 5 μ L of the diluted compounds were added to the wells.
15 Thirty μ L of substrate solution (7 mM NADPH (Sigma N1630), 3.35 μ M 17-OH-pregnenolone (Steraloids Q4710), 3.35 μ g/mL human cytochrome b₅ (Panvera P2252) in 50 mM sodium phosphate pH 7.5 buffer) was added to all wells. Reactions were initiated with the addition of 10 μ L hLyase or mLyase in assay buffer.

Enzymatic reactions were allowed to run for 2 h at rt with gentle agitation. Reactions
20 were terminated with the addition of 50 μ M (final concentration) YM116, a potent C17,20 lyase inhibitor. The concentration of DHEA generated by hLyase was determined by
radioimmunoassay (RIA) as described below.

0.08 μ Ci ³H-DHEA (1.6 μ Ci/mL) (NEN (NET814)) in scintillation proximity assay (SPA) buffer (100 mM Tris-HCl, pH 7.5, 50 mM NaCl, 0.5% BSA (Sigma A9647), 0.2%
25 Tween 20) was added to each well. Fifty μ L DHEA rabbit antiserum with anti-rabbit SPA beads in SPA buffer was added to all wells. Anti DHEA rabbit antiserum was obtained from Endocrine Sciences (D7-421) (1 mL H₂O to the vial) and anti-Rabbit SPA Beads were obtained from Amersham (RPNQ 0016) (6mL SPA buffer to the bottle). Mixtures were allowed to equilibrate with gentle agitation for 1 h followed by an overnight equilibration
30 with no agitation. ³H-DHEA bound to the SPA beads was determined by scintillation counting.

The concentration of DHEA generated in each reaction was calculated from raw data (CPM) and the standard curve. The lyase inhibitory activity of each compound was determined as the concentration of DHEA generated in the presence of test compounds, expressed as a percent inhibition compared to the DHEA concentration generated in the absence of test compounds ($1 - (\text{nM DHEA formed in the presence of test compound} / \text{nM DHEA formed in the absence of test compounds}) \times 100$).

Human C17,20 cellular assay:

Human 293 lyase cells were prepared as described above for the Sf9 cells [Baculovirus Expression of Bovine Cytochrome P₄₅₀ in Sf9 Cells and Comparison with Expression in Yeast, Mammalian Cells, and *E. Coli*. Barnes, H. J.; Jenkins, C. M.; Waterman, M. R. *Archives of Biochemistry and Biophysics* (1994) 315 (2) 489-494]. The cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) /10% FBS/1% S/P/1% L-Glu/0.8mg/mL G418/HEPES.

On day one, human 293 lyase cells were plated at 10,000 cells/well/100 μ L in columns 2-12 of a 96-well tissue culture plate (Falcon 3075), and allowed to attach overnight (each mother plate needs two cell plates).

On day two, 100 μ L H₂O was added to all the wells of a daughter plate (one mother plate one daughter plate Costar 3365). DHEA standard was diluted with RPMI (4.5 μ L of 500 μ M into 3 mL RPMI, then 1:3 serial dilutions). The media from columns 2-12 of the cell plate was removed and replaced with 100 μ L RPMI without phenol red. Diluted DHEA standards (100 μ L) at a concentration of 750, 250, 83.3, 27.7, 9.2, 3, 1 and 0.3 nM were added to column 1 of the cell plate. 50 μ L of 100% DMSO was added to columns 1 and 2 of the mother plate. 5 μ L of compound was transferred from mother plate to daughter plate, then from the daughter plate to a cell plate using a robot. The cell plate was incubated for 10 min at rt. 15 μ L of 10 mM 17-OH-pregnenolone (Steraloids (Q4710) (10 mM stock in 100% DMSO)) was diluted in 30 mL RPMI to obtain a solution of 5 μ M 17-OH-pregnenolone. 10 μ L of this solution was added to all the wells of the cell plate, except that column received only DMSO. The plate was then incubated for one h at 37°C.

The amount of DHEA produced was determined as follows. 90 μ L media was removed from each well of the cell plate and placed into an SPA assay plate (Wallac Isoplate #1450). 50 μ L of ³H-DHEA (1.6 μ Ci/mL, New England Nuclear (Catalog # NET814)) was

added to each well of the SPA assay plate. 50 μ L of anti-DHEA/anti-rabbit SPA beads (20 μ L/mL AB with 10 mg/mL SPA beads) were then added to each well of the plate. The plate was incubated overnight, and the radioactivity counted as described above. The first two columns of the plate were reserved for a standard curve of DHEA and the no compound controls.

The raw data (CPM) was converted to a concentration of DHEA formed (nM) by use of the standard curve. The lyase inhibitory activity of the compounds was determined as the amount of DHEA formed in the presence of compound compared to the amount formed in the absence of compound in the form of a percent inhibition ($1 - (\text{nM DHEA formed with compound} / \text{nM DHEA formed without compound}) \times 100$).

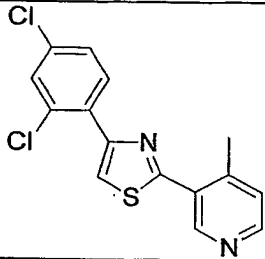
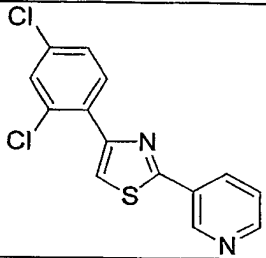
A test compound was considered to be active if the IC_{50} in the human C17,20 biochemical assay or in the human C17,20 cellular assay was less than 10 μ M. All the compounds tested have IC_{50} in the human C17,20 biochemical assay or the human C17,20 cellular assay of less than 10 μ M.

Comparative testing

The inhibitory activity of 2-[4-methyl-3-pyridyl]-4-(2,4-dichlorophenyl)thiazole was compared to that of 2-(3-pyridyl)-4-(2,4-dichlorophenyl)thiazole, described in EP 411,718. Against C17,20 human lyase, 4-methyl substituted pyridines have been consistently more active than 4-unsubstituted pyridines. In the present case, 2-[4-methyl-3-pyridyl]-4-(2,4-dichlorophenyl)thiazole has an inhibitory IC_{50} of 15 nM, whereas 2-(3-pyridyl)-4-(2,4-dichlorophenyl)thiazole has an inhibitory IC_{50} of 406 nM. Surprisingly and unexpectedly, when both compounds were tested against powdery mildew, a fungal species identified in EP 411,718, 2-(3-pyridyl)-4-(2,4-dichlorophenyl)thiazole showed 80% inhibition whereas 2-[4-methyl-3-pyridyl]-4-(2,4-dichlorophenyl)thiazole was devoid of activity.

*Statistically insignificant

Table V-Comparitive Test Data

Structure	Human Lyase IC ₅₀	Mouse Lyase IC ₅₀	% Inhibition against Powdery Mildew
	1.51E-08	3.97E-08	10%*
	4.06E-07	1.40E-06	80%

5

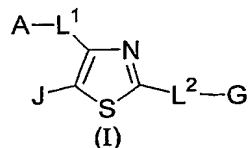
Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS:

We claim

1. A compound of the formula (I)



5 wherein

L^1 represents

a chemical bond;

carbonyl;

$-(CH_2)_a-$ wherein

10 a is 1, 2, or 3;

$-CH_2O-$;

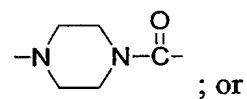
$-OCH_2-$;

$-O-$;

$-N(R^1)-$ wherein

15 R^1 represents H or C_{1-4} alkyl;

$-NHC(O)-$;



$-CH_2NHC(O)-$;

20 L^2 represents

a chemical bond;

$-(CH_2)_a-$;

$-CH_2O-$;

$-N(R^1)-$; or

25 $-NH(CH_2)_a-$;

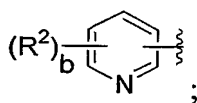
J represents

H;

C_{1-4} alkyl; or

30 halogen; and

1) when L^1 is a chemical bond, A represents



wherein

b is 0, 1, or 2; and

R^2 is selected from

C_{1-6} alkyl;

C_{1-4} haloalkyl;

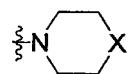
OR^1 ;

C_{3-6} cycloalkyl;

halogen;

phenyl optionally substituted by halogen;

NO_2 ;



; wherein

X represents CH_2 , O, S, or $N(R^1)$;

$-N(R^3)_2$; wherein

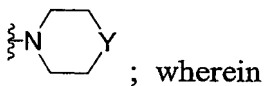
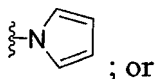
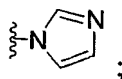
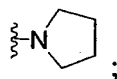
R^3 represents H, C_{1-4} alkyl, C_{4-6} cycloalkyl, or phenyl
optionally substituted by halogen;

$-(CH_2)_a N(R^1)(R^4)$ wherein

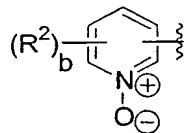
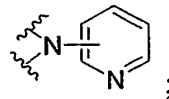
R^4 represents $-(CH_2)_a OR^1$ or $-(CH_2)_a N(R^1)_2$; and

$-(CH_2)_a R^5$; wherein

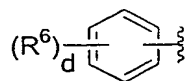
R^5 represents



Y represents $N(R^1)$, O, S, or



- , provided that G is other than a pyridyl or an N-oxide-containing group;



- ; wherein

d is 0, 1, or 2 ;

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; wherein

R^7 represents H, C_{1-4} alkyl, C_{1-4} haloalkyl, phenyl, benzyl, or pyridyl optionally substituted by C_{1-3} haloalkyl;

halogen;

NO_2 ;

CN;

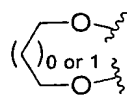
CO_2R^1 ;

~~C_{1-4} acyl;~~

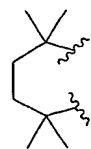
phenyl optionally substituted by halogen ;

benzyl ;

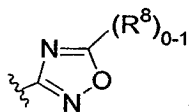
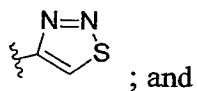
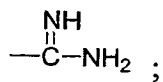
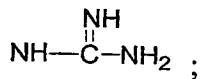
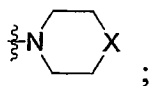
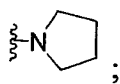
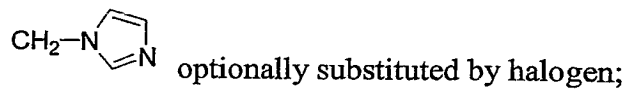
$N(R_1)^2$;



wherein the O atoms are bonded to the phenyl ring at adjacent carbons;

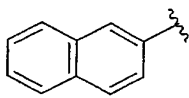


wherein the terminal carbons are bonded to the phenyl ring at adjacent carbons;

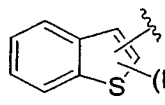
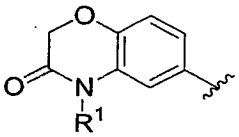
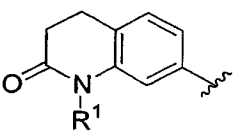


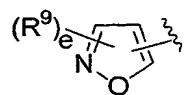
wherein R^8 represents C_{1-4} alkyl or phenyl optionally substituted by halogen;

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-  ;
- C_{3-8} cycloalkyl ;
- C_{5-6} cycloalkenyl ;
- adamantyl ;
- norbornyl;

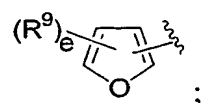
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-  ;
-  ;
-  ;
- $\text{N(R}^1)_2$;

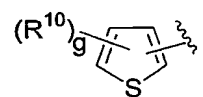


; wherein

e is 0, 1, or 2;

R⁹ represents C₁₋₄ alkyl or phenyl optionally substituted by halogen;

5

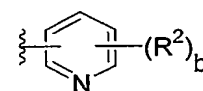


; wherein

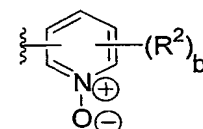
g is 0, 1, or 2; and

R¹⁰ represents CN, NO₂, or halogen;

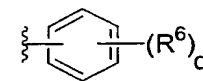
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2) when L² is a bond, G represents

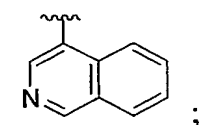
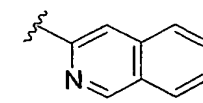
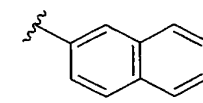
or;

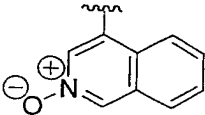


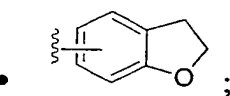
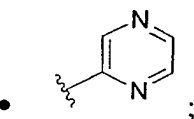
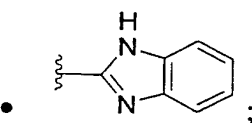
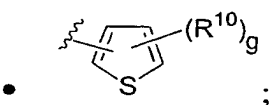
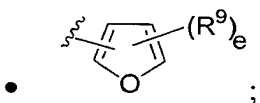
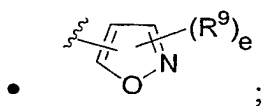
, provided that A is other than a pyridyl or an N-oxide-containing group;

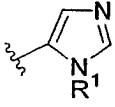
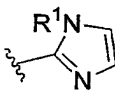
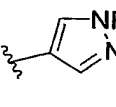
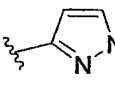


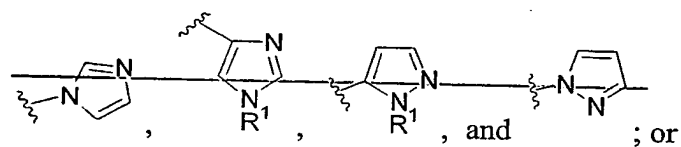
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-  , provided that A is other than a pyridyl or an N-oxide-containing group;

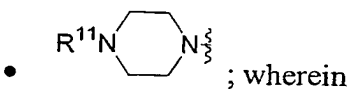
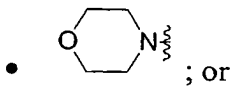
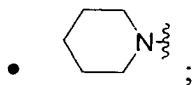


- a diazole selected from  ,  ,  ,  ,



- a triazole;

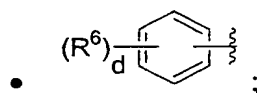
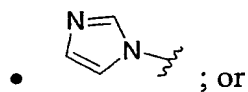
3) when L¹ is carbonyl, A represents



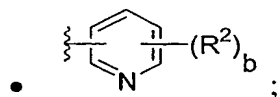
R^{11} represents H, C_{1-4} alkyl, or phenyl optionally substituted by halogen;

4) when L^1 is $-(CH_2)_a-$, A represents

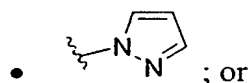
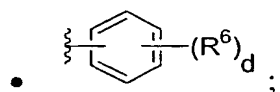
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5) when L^2 is $-(CH_2)_a-$, G represents



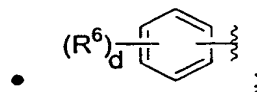
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- a triazole;

6) when L^1 is $-CH_2O-$, $-OCH_2-$ or O, A represents

15



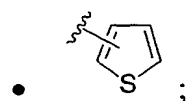
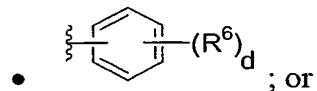
- $-C_{1-4}$ -alkyl;

- C_{3-8} cycloalkyl; or

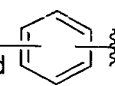
- C_{6-7} bicycloalkyl;

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7) when L^2 is $-CH_2O-$, G represents

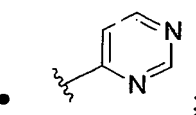
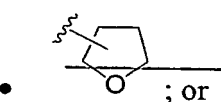
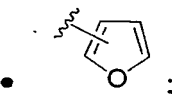
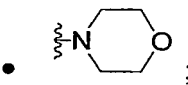
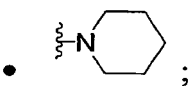
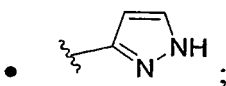
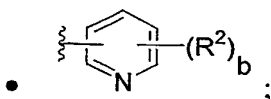
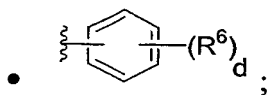


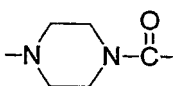
8) when L^1 is $-N(R^1)-$, A represents

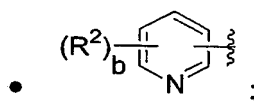
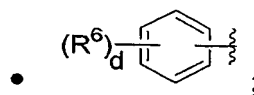
- $(R^6)_d$  ; or
- C₅₋₆ cycloalkyl;

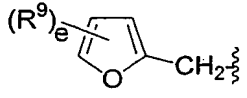
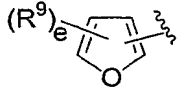
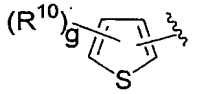
9) when L² is -N(R¹)- or -NH(CH₂)_a-, G represents

- C₁₋₆ alkyl;
- C₃₋₆ cycloalkyl;
- N(R¹)₂;



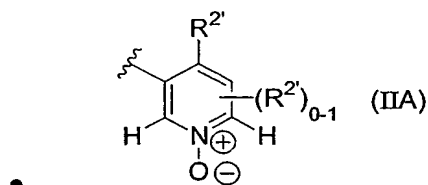
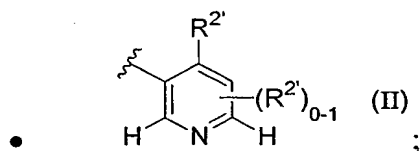
10) when L¹ is -NHC(O)-, , or -CH₂NHC(O)-, A represents



- C₅₋₆ cycloalkyl;
- C₇₋₈ bicycloalkyl;
-  ;
-  ; or
-  ;

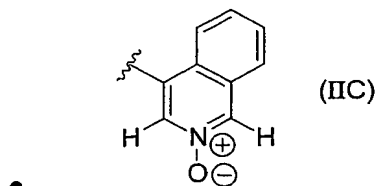
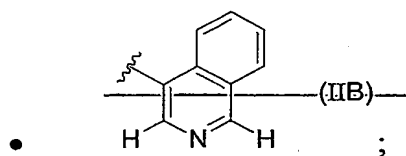
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- 11) one of A and G is a 3-pyridyl moiety of formula (II) or (IIA), or a 4-isoquinolinyl moiety of formula (IIB) or (IIC)



10

- , provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;



- , provided that the other of A and G is other than a pyridyl or an N-oxide-containing group;

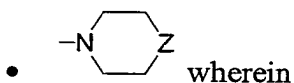
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which is joined to the thiazole ring via a chemical bond L¹ or L² respectively; and the other of A and G is as defined above; and

furthermore, when the other of A and G is joined to the thiazole ring via linker L^1 or L^2 respectively where L^1 or L^2 is not a chemical bond, then $R^{2'}$ of formulae (II) and (IIA) is R^2 ; but when each of A and G is joined to the thiazole ring via a chemical bond L^1 and L^2 respectively, then $R^{2'}$ of formulae (II) and (IIA) is selected from the group consisting of

- C_{2-6} alkyl, provided that when said 3-pyridyl moiety of formula (II) constitutes A, then G is other than phenyl substituted with an amide or sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F;

- C_{2-4} haloalkyl;
- C_{4-6} alkoxy;
- C_{3-6} cycloalkyl;
- phenyl optionally substituted by halogen;



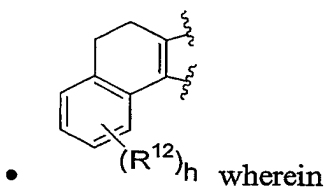
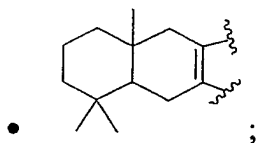
Z represents CH_2 , S, or $N(R^1)$

- $-N(R^{3'})_2$ wherein

$R^{3'}$ represents H, C_{3-4} alkyl, C_{4-6} cycloalkyl, or phenyl optionally substituted with halogen;

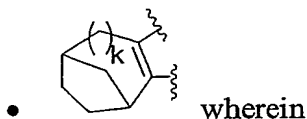
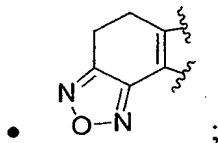
- $-(CH_2)_a N(R^1)(R^4)$;
- $-(CH_2)_a R^5$;

12) alternatively, A- L^1 and J may be joined and together with the carbon atoms to which they are connected form a ring moiety selected from the group consisting of

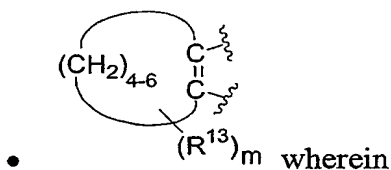


h is 0, 1, or 2; and

R^{12} represents C_{1-4} alkyl or C_{1-4} alkoxy;



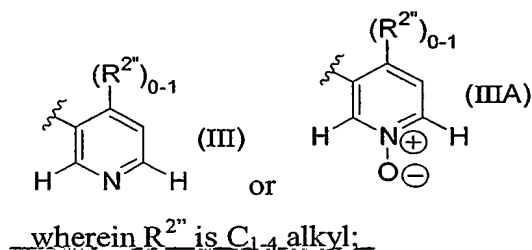
k is 0 or 1; or



m is 0, 1, or 2;

R^{13} represents C_{1-4} alkyl or phenyl;

said ring moiety being joined to the thiazole at the positions indicated by the truncated valences shown in the partial structures above to form a fused ring thiazole; and for these fused ring thiazoles, L^2 is a bond and G is a 3-pyridyl moiety of formula (III) or (IIIA)



or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1

wherein

L^1 represents

a chemical bond;

carbonyl;

$-(CH_2)_a-$

$-OCH_2-$;

L^2 represents

a chemical bond;

$-(CH_2)_a-$; or

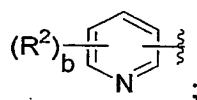
$-N(R^1)-$;

J represents

H; or

C_{1-4} alkyl;

1) when L^1 is a chemical bond, A represents



wherein

R^2 is selected from

C_{1-6} alkyl;

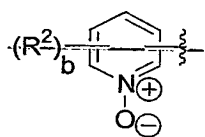
C_{1-4} haloalkyl;

C_{3-6} cycloalkyl;

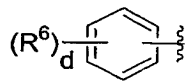
halogen;

phenyl optionally substituted by halogen; and

$-(CH_2)_aR^5$;



containing group;



R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; wherein

R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

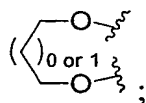
halogen;


NO₂;

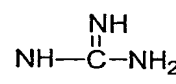
CN;

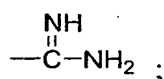
CO₂R¹;

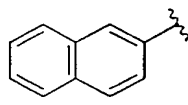
C₁₋₄ acyl;



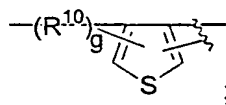
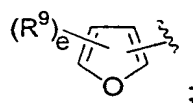
CH₂-N  optionally substituted by halogen;

; and

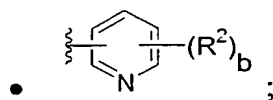
;



- C₃₋₈ cycloalkyl;
- C₅₋₆ cycloalkenyl;
- adamantyl;
- norbornyl;



2) when L² is a bond, G represents



wherein

R² is selected from

C₁₋₆ alkyl;

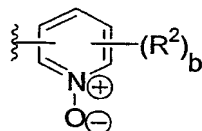
C₁₋₄ haloalkyl;

C₃₋₆ cycloalkyl;

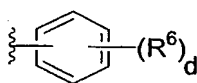
halogen;

phenyl optionally substituted by halogen; and

$-(CH_2)_aR^5$;



- , provided that A is other than a pyridyl or an N-oxide-containing group;



- ; wherein

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ;

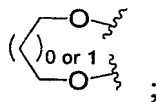
halogen;


NO_2 ;

CN;

CO_2R^1 ;

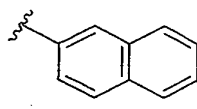
C_{1-4} acyl ;



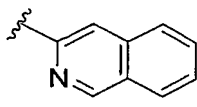
CH_2-N  optionally substituted by halogen;

$NH-C(=NH)-NH_2$; and

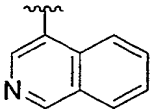
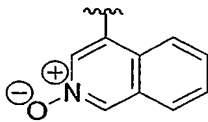
$-C(=NH)-NH_2$;

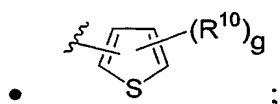


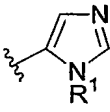
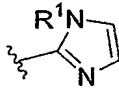
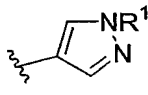
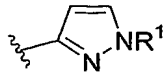
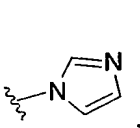
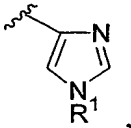
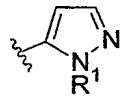
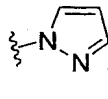
- ;



- ;

-  ;
-  , provided that A is other than a pyridyl or an N-oxide-containing group;



- a diazole selected from  ,  ,  ,  ,  ,  ,  , and  ; or
- a triazole;

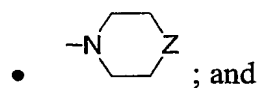
and

when each of A and G is joined to the thiazole ring via a chemical bond L¹ and L² respectively, then R^{2'} of formulae (II) and (IIA) is selected from the group consisting of

- C₂₋₆ alkyl, provided that when said 3-pyridyl moiety of formula (II)

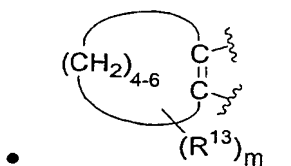
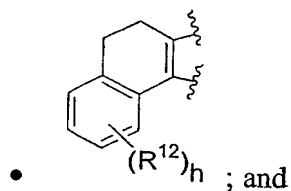
constitutes A, then G is other than phenyl substituted with an amide or sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F;

- C₃₋₆ cycloalkyl;
- phenyl optionally substituted by halogen;



- -(CH₂)_aR⁵ ; and

12) A-L¹ and J may be joined and together with the carbon atoms to which they are connected form a ring moiety selected from the group consisting of



5

3. A compound according to claim 1
wherein

L¹ represents

10 a chemical bond;
-(CH₂)_a-
-OCH₂- ;

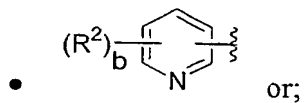
L² represents

15 a chemical bond;
-(CH₂)_a- ; or
-N(R¹)-;

J represents H;

20

1) when L¹ is a chemical bond, A represents



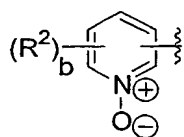
wherein

R² is selected from

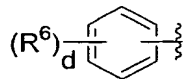
25

C₁₋₆ alkyl;
C₁₋₄ haloalkyl;

C₃₋₆ cycloalkyl; and
phenyl optionally substituted by halogen;



- , provided that G is other than a pyridyl or an N-oxide-containing group;



- ; wherein

R⁶ is selected from

C₁₋₆ alkyl ;

C₁₋₄ haloalkyl ;

OR⁷ ; wherein

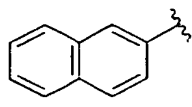
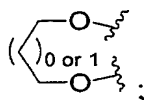
R⁷ represents C₁₋₄ alkyl or C₁₋₄ haloalkyl;

halogen;

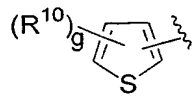
NO₂ ;

CN;

CO₂R¹ ; and

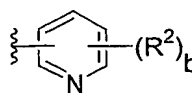


- ;
- C₃₋₈ cycloalkyl ;
- C₅₋₆ cycloalkenyl ;
- adamantyl ; or



- ;

2) when L² is a bond, G represents



- or ;

wherein

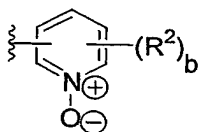
R^2 is selected from

C_{1-6} alkyl;

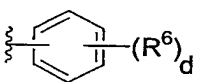
C_{1-4} haloalkyl;

C_{3-6} cycloalkyl; and

phenyl optionally substituted by halogen;



, provided that A is other than a pyridyl or an N-oxide-containing group;



; wherein

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

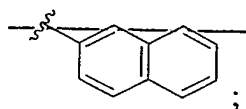
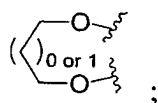
OR^7 ;

halogen;

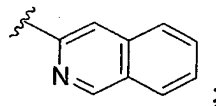
NO_2 ;

CN ;

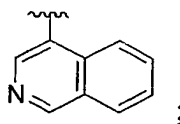
CO_2R^1 ; and



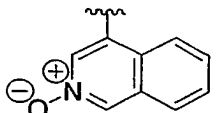
;



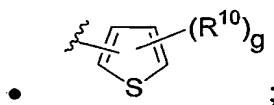
;



;



, provided that A is other than a pyridyl or an N-oxide-containing group; or



and

when each of A and G is joined to the thiazole ring via a chemical bond L^1 and L^2 respectively, then $R^{2'}$ of formulae (II) and (IIA) is selected from the group consisting of

- C_{2-6} alkyl, provided that when said 3-pyridyl moiety of formula (II) constitutes A, then G is other than phenyl substituted with an amide or sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F;
- C_{3-6} cycloalkyl; and
- phenyl optionally substituted by halogen.

4. A compound according to claim 1

wherein

L^1 represents

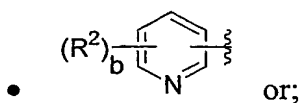
a chemical bond;

L^2 represents

a chemical bond;

J represents H;

1) A represents



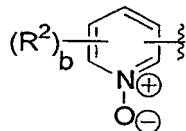
wherein

R^2 is selected from

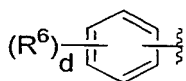
C₁₋₆ alkyl;

C₃₋₆ cycloalkyl; and

phenyl optionally substituted by halogen;



- , provided that G is other than a pyridyl or an N-oxide-containing group;



; wherein

R⁶ is selected from

C₁₋₆ alkyl ;

C₁₋₄ haloalkyl ;

OR⁷ ; wherein

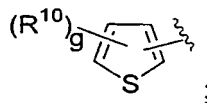
R⁷ represents C₁₋₄ alkyl or C₁₋₄ haloalkyl;

halogen;

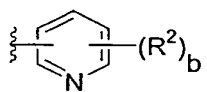
NO₂ ; and

CN;

or



~~-2)-G.represents-~~



or ;

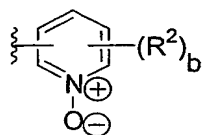
wherein

R² is selected from

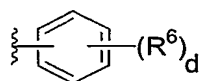
C₁₋₆ alkyl;

C₃₋₆ cycloalkyl; and

phenyl optionally substituted by halogen;



- , provided that A is other than pyridyl or an N-oxide-containing group;



- ; wherein

R^6 is selected from

C_{1-6} alkyl ;

C_{1-4} haloalkyl ;

OR^7 ; wherein

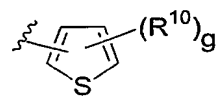
R^7 represents C_{1-4} alkyl or C_{1-4} haloalkyl;

halogen;

NO_2 ;

CN ;

or



- ;

and

when each of A and G is joined to the thiazole ring via a chemical bond L^1 and L^2 respectively, then $R^{2'}$ of formulae (II) and (IIA) is selected from the group consisting of

- C_{2-6} alkyl, provided that when said 3-pyridyl moiety of formula (II) constitutes A, then G is other than phenyl substituted with an amide or sulfonamide group; and when said 3-pyridyl moiety of formula (II) constitutes G, then A is other than phenyl substituted with F;

and

- C_{3-6} cycloalkyl.

5. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

6. A method of inhibiting a lyase enzyme, comprising contacting said lyase enzyme with a compound of claim 1.
- 5 7. A method of inhibiting a 17α -hydroxylase-C17,20 lyase, comprising contacting a 17α -hydroxylase-C17,20 lyase with a compound of claim 1.
8. A method for treating a subject having a cancer associated with a 17α -hydroxylase-C17,20 lyase, comprising administering to the subject a therapeutically effective
10 amount of a compound of claim 1.
9. A method for treating prostate cancer in a subject, comprising administering to said subject a therapeutically effective amount of a compound of claim 1, such that the prostate cancer in the subject is treated.
15
10. A method for treating breast cancer in a subject, comprising administering to said subject a therapeutically effective amount of a compound of claim 1, such that the breast cancer in the subject is treated.
- 20 11. The method of any one of claims 8-10, wherein said subject is a primate, equine, canine or feline.
12. The method of any one of claims 8-10, wherein said subject is a human.

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 3-PYRIDYL OR 4-ISOQUINOLINYL THIAZOLES AS C17,20 LYASE INHIBITORS

(57) Abstract: The invention provides novel thiazoles bearing 3-pyridyl or 4-isoquinilnyl substituents, and pharmaceutical compositions thereof. The invention also provides methods of using compounds of the invention and pharmaceutical compositions thereof as inhibitors of lyases, e.g., the 17 α -hydroxylase-C17,20 enzyme. The invention further provides methods for treating cancer in a subject, comprising administering to the subject a compound of the invention or a pharmaceutical composition thereof. The cancer can be, e.g., prostate cancer or breast cancer.



WO 03/027085 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/30483

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/14 C07D417/04 A61P35/00 //(C07D417/04,277:00,
213:00),(C07D417/14,277:00,265:00,213:00),(C07D417/14,333:00,
277:00,213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search

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